EXAMPLE 123: Isolation of cDNA clones Encoding Human PRO1287

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to the fringe protein. This EST sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence obtained is herein designated DNA40568.

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Based on the DNA40568 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1287. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

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forward PCR primer 5'-CTCGGGGAAAGGGACTTGATGTTGG-3' (SEQ ID NO:382)

reverse PCR primer 1 5'-GCGAAGGTGAGCCTCTATCTCGTGCC-3' (SEQ ID NO:383)

reverse PCR primer 2 5'-CAGCCTACACGTATTGAGG-3' (SEQ ID NO:384)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40568 sequence which had the following nucleotide sequence

25 <u>hybridization probe</u>

5'-CAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTCCC-3' (SEQ ID NO:385).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1287 gene using the probe oligonucleotide and one of the PCR primers.

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RNA for construction of the cDNA libraries was isolated from human bone marrow tissue. The cDNA libraries used to isolated the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1287 (designated herein as DNA61755-1554 [Figure 275, SEQ ID NO:380]) and the derived protein sequence for PRO1287.

The entire nucleotide sequence of DNA61755-1554 is shown in Figure 275 (SEQ ID NO:380). The full length clone contained a single open reading frame with an apparent translational initiation site at nucleotide positions 655-657 and a stop signal at nucleotide positions 2251-2253 (Figure 275, SEQ ID NO:380). The predicted polypeptide precursor is 532 amino acids long, has a calculated molecular weight of approximately 61,351 daltons and an estimated pI of approximately 8.77. Analysis of the full-length PRO1287 sequence shown in Figure 276 (SEQ ID NO:381) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 27 and potential N-glycosylation sites from about amino acid 315 to about amino acid 318 and from about amino acid 324 to about amino acid 327. Clone DNA61755-1554 has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203112.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 276 (SEQ ID NO:381), evidenced significant homology between the PRO1287 amino acid sequence and the following Dayhoff sequences: CET24D1_1, EZRI_BOVIN, GGU19889_1, CC3_YEAST, S74244, NALS_MOUSE, MOES_PIG, S28660, S44860 and YNA4 CAEEL.

EXAMPLE 124: Isolation of cDNA clones Encoding Human PRO1312

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DNA55773 was identified in a human fetal kidney cDNA library using a yeast screen that preferentially represents the 5' ends of the primary cDNA clones. Based on the DNA55773 sequence, oligonucleotides were synthesized for use as probes to isolate a clone of the full-length coding sequence for PRO1312.

The full length DNA61873-1574 clone shown in Figure 277 (SEQ ID NO:386) contained a single open reading frame with an apparent translational initiation site at nucleotide positions 7-9 and ending at the stop codon found at nucleotide positions 643-645. The predicted polypeptide precursor is 212 amino acids long (Figure 278, SEQ ID NO:387). PRO1312 has a calculated molecular weight of approximately 24,024 daltons and an estimated pl of approximately 6.26. Other features include a signal peptide at about amino acids 1-14; a transmembrane domain at about amino acids 141-160, and potential N-glycosylation sites at about amino acids 76-79 and 93-96.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 278 (SEQ ID NO:387), revealed some homology between the PRO1312 amino acid sequence and the following Dayhoff sequences: GCINTALPH_1, GIBMUC1A_1, P_R96298, AF001406_1, PVU88874_1, P_R85151, AF041409_1, CELC50F2_7, C45875, and AB009510_21.

Clone DNA61873-1574 has been deposited with ATCC and is assigned ATCC deposit no. 203132.

EXAMPLE 125: Isolation of cDNA clones Encoding Human PRO1192

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein DNA35924. Based on the DNA35924 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1192.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-CCGAGGCCATCTAGAGGCCAGAGC-3' (SEQ ID NO:390)

reverse PCR primer: 5'-ACAGGCAGAGCCAATGGCCAGAGC-3' (SEQ ID NO:391).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35924 sequence which had the following nucleotide sequence:

hybridization probe:

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5'-GAGAGGACTGCGGGAGTTTGGGACCTTTGTGCAGACGTGCTCATG-3' (SEQ ID NO:392).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1192 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver and spleen tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1192 designated herein as DNA62814-1521 and shown in Figure 279 (SEQ ID NO:388); and the derived protein sequence for PRO1192 which is shown in Figure 280 (SEQ ID NO:389).

The entire coding sequence of PRO1192 is shown in Figure 279 (SEQ ID NO:388). Clone DNA62814-1521 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and an apparent stop codon at nucleotide positions 766-768. The predicted polypeptide precursor is 215 amino acids long. The predicted polypeptide precursor has the following features: a signal peptide at about amino acids 1-21; a transmembrane domain at about amino acids 153-176; potential N-glycosylation sites at about amino acids 39-42 and 118-121; and homology with myelin P0 proteins at about amino acids 27-68 and 99-128 of Figure 280. The full-length PRO1192 protein shown in Figure 280 has an estimated molecular weight of about 24,484 daltons and a pI of about 6.98.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 280 (SEQ ID NO:389), revealed homology between the PRO1192 amino acid sequence and the following Dayhoff sequences: GEN12838, MYP0_HUMAN, AF049498_1, GEN14531, P_W14146, HS46KDA_1, CINB_RAT, OX2G_RAT, D87018 1, and D86996 2.

Clone DNA62814-1521 was deposited with the ATCC on August 4, 1998, and is assigned ATCC deposit no. 203093.

EXAMPLE 126: Isolation of cDNA clones Encoding Human PRO1160

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described

in Example 1 above This consensus sequence is herein designated DNA40650. Based on the DNA40650 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1160.

PCR primers (forward and reverse) were synthesized:

5 <u>forward PCR primer</u> 5'-GCTCCCTGATCTTCATGTCACCACC-3' (SEQ ID NO:395)

reverse PCR primer 5'-CAGGGACACACTCTACCATTCGGGAG-3' (SEQ ID NO:396)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40650 sequence which had the following nucleotide sequence

hybridization probe

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10 5'-CCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTC-3' (SEQ ID NO:397)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1160 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human breast tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1160 (designated herein as DNA62872-1509 [Figure 281, SEQ ID NO: 393]) and the derived protein sequence for PRO1160.

The entire nucleotide sequence of DNA62872-1509 is shown in Figure 281 (SEQ ID NO:393). Clone DNA62872-1509 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 40-42 and ending at the stop codon at nucleotide positions 310-312 (Figure 281). The predicted polypeptide precursor is 90 amino acids long (Figure 282). The full-length PRO1160 protein shown in Figure 282 has an estimated molecular weight of about 9,039 daltons and a pI of about 4.37. Analysis of the full-length PRO1160 sequence shown in Figure 282 (SEQ ID NO:394) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19 and a protein kinase C phosphorylation site from about amino acid 68 to about amino acid 70. Clone DNA62872-1509 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203100.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 282 (SEQ ID NO:394), evidenced significant homology between the PRO1160 amino acid sequence and the following Dayhoff sequences: B30305, GEN13490, I53641, S53363, HA34_BRELC, SP96_DICDI, S36326, SSU51197_10, MUC1_XENLA, TCU32448_1 and AF000409_1.

EXAMPLE 127: Isolation of cDNA clones Encoding Human PRO1187

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing

homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57726.

In light of an observed sequence homology between the DNA57726 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 358563, the Incyte EST clone 358563 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 283 and is herein designated as DNA62876-1517.

The full length clone shown in Figure 283 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and ending at the stop codon found at nucleotide positions 481-483 (Figure 283; SEQ ID NO:398). The predicted polypeptide precursor (Figure 284, SEQ ID NO:399) is 120 amino acids long. The signal peptide is at about amino acids 1-17 of SEQ ID NO:399. PRO1187 has a calculated molecular weight of approximately 12,925 daltons and an estimated pl of approximately 9.46. Clone DNA62876-1517 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203095. It is understood that the deposited clone contains the actual sequence and that the representations herein may have minor sequencing errors.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 284 (SEQ ID NO:399), revealed some sequence identity (and therefore some relation) between the PRO1187 amino acid sequence and the following Dayhoff sequences: MGNENDOBX_1, CELF41G3_9, AMPG_STRLI, HSBBOVHERL_2, LEEXTEN10_1, AF029958_1 and P_W04957.

EXAMPLE 128: Isolation of cDNA clones Encoding Human PRO1185

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Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56426.

In light of an observed sequence homology between the DNA56426 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3284411, the Incyte EST clone 3284411 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 285 and is herein designated as DNA62881-1515.

The full length DNA62881-1515 clone shown in Figure 285 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 4-6 and ending at the stop codon found at nucleotide positions 598-600 (Figure 285; SEQ ID NO:400). The predicted polypeptide precursor (Figure 286, SEQ ID NO:401) is 198 amino acids long. The signal peptide is at about amino acids 1-21 of SEQ ID NO:401. PRO1185 has a calculated molecular weight of approximately 22,105 daltons and an estimated pI of approximately 7.73. Clone DNA62881-1515 has been deposited with the ATCC and is assigned ATCC deposit no. 203096.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 286 (SEQ ID NO:401), revealed some sequence identity between the PRO1185 amino acid sequence and the following Dayhoff sequences: TUP1_YEAST, AF041382_1, MAOM_SOLTU, SPPBPHU9_1,I41024, EPCPLCFAIL_1, HSPLEC_1, YKL4_CAEEL, A44643, TGU65922 1.

EXAMPLE 129: Isolation of cDNA clones Encoding Human PRO1345

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA47364. Based on the DNA47364 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1345.

PCR primers (forward and reverse) were synthesized:

20 <u>forward PCR primer</u> 5'-CCTGGTTATCCCCAGGAACTCCGAC-3' (SEQ ID NO:404) <u>reverse PCR primer</u> 5'-CTCTTGCTGCTGCGACAGGCCTC-3' (SEQ ID NO:405)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47364 sequence which had the following nucleotide sequence

hybridization probe

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25 5'-CGCCCTCCAAGACTATGGTAAAAGGAGCCTGCCAGGTGTCAATGAC-3' (SEQ ID NO:406)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1345 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human breast carcinoma tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1345 (designated herein as DNA64852-1589 [Figure 287, SEQ ID NO:402]) and the derived protein sequence for PRO1345.

The entire nucleotide sequence of DNA64852-1589 is shown in Figure 287 (SEQ ID NO:402). Clone DNA64852-1589 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 7-9 or 34-36 and ending at the stop codon at nucleotide positions 625-627 (Figure 287). The predicted polypeptide precursor is 206 amino acids long (Figure 288). The full-length PRO1345 protein shown in Figure 288 has an estimated molecular weight of about 23,190 daltons and a pl of about 9.40. Analysis of

the full-length PRO1345 sequence shown in Figure 288 (SEQ ID NO:403) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31 or from about amino acid 10 to about amino acid 31 and a C-type lectin domain signature sequence from about amino acid 176 to about amino acid 190. Clone DNA64852-1589 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203127.

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An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 288 (SEQ ID NO:403), evidenced significant homology between the PRO1345 amino acid sequence and the following Dayhoff sequences: BTU22298_1, TETN_CARSP, TETN_HUMAN, MABA_RAT, S34198, P_W13144, MACMBPA_1, A46274, PSPD_RAT AND P_R32188.

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EXAMPLE 130: Isolation of cDNA clones Encoding Human PRO1245

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56019.

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In light of an observed sequence homology between the DNA56019 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1327836, the Incyte EST clone 1327836 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 289 and is herein designated as DNA64884-1527.

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The full length clone shown in Figure 289 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 79-81 and ending at the stop codon found at nucleotide positions 391-393 (Figure 289; SEQ ID NO:407). The predicted polypeptide precursor (Figure 290, SEQ ID NO:408) is 104 amino acids long, with a signal peptide sequence at about amino acid 1 to about amino acid 18. PRO1245 has a calculated molecular weight of approximately 10,100 daltons and an estimated pl of approximately 8.76.

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An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 290 (SEQ ID NO:408), revealed some homology between the PRO1245 amino acid sequence and the following Dayhoff sequences: SYA_THETH, GEN11167, MTV044_4, AB011151_1, RLAJ2750_3, SNELIPTRA_1, S63624, C28391, A37907, and S14064.

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Clone DNA64884-1245 was deposited with the ATCC on August 25, 1998 and is assigned ATCC deposit no. 203155.

EXAMPLE 131: Isolation of cDNA clones Encoding Human PRO1358

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

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In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 88718, the Incyte EST clone 88718 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 291 and is herein designated as DNA64890-1612.

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The full length clone shown in Figure 291 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 86 through 88 and ending at the stop codon found at nucleotide positions 1418 through 1420 (Figure 291; SEQ ID NO:409). The predicted polypeptide precursor (Figure 292, SEQ ID NO:410) is 444 amino acids long. The signal peptide is at about amino acids 1-18 of SEQ ID NO:410. PRO1358 has a calculated molecular weight of approximately 50,719 daltons and an estimated pI of approximately 8.82. Clone DNA64890-1612 was deposited with the ATCC on August 18, 1998 and is assigned ATCC deposit no. 203131.

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An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 292 (SEQ ID NO:410), revealed sequence identity between the PRO1358 amino acid sequence and the following Dayhoff sequences: P_W07607, AB000545_1, AB000546_1, A1AT_RAT, AB015164_1, P_P50021, COTR_CAVPO, and HAMHPP_1. The variants claimed in this application exclude these sequences.

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EXAMPLE 132: Isolation of cDNA clones Encoding Human PRO1195

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55716.

In light of an observed sequence homology between the DNA55716 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3252980, the Incyte EST clone 3252980 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 293 and is herein designated as DNA65412-1523.

The full length clone shown in Figure 293 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon found at nucleotide positions 511-513 (Figure 293; SEQ ID NO:411). The predicted polypeptide precursor (Figure 294, SEQ ID NO:412) is 151 amino acids long. The signal sequence is at about amino acids 1-22 of SEQ ID NO:412. PRO1195 has a calculated molecular weight of approximately 17,277 daltons and an estimated pI of approximately 5.33. Clone DNA65412-1523 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203094.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 294 (SEQ ID NO:412), revealed some sequence identity between the PRO1195 amino acid sequence and the following Dayhoff sequences: MMU28486_1, AF044205_1, P_W31186, CELK03C7_1, F69034, EF1A_METVA, AF024540_1, SSU90353_1, MRSP STAAU and P R97680.

EXAMPLE 133: Isolation of cDNA clones Encoding Human PRO1270

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Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57951.

In light of an observed sequence homology between the DNA57951 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 124878, the Merck EST clone 124878 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 295 and is herein designated as DNA66308-1537.

Clone DNA66308-1537 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 103-105 and ending at the stop codon at nucleotide positions 1042-1044 (Figure 295). The predicted polypeptide precursor is 313 amino acids long (Figure 296). The full-length PRO1270 protein shown in Figure 296 has an estimated molecular weight of about 34,978 daltons and a pI of about 5.71. Analysis of the full-length PRO1270 sequence shown in Figure 296 (SEQ ID NO:414) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 16, a potential N-glycosylation site from about amino acid 163 to about amino acid 166 and glycosaminoglycan attachment sites from about

amino acid 74 to about amino acid 77 and from about amino acid 289 to about amino acid 292. Clone DNA66308-1537 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203159.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 296 (SEQ ID NO:414), evidenced significant homology between the PRO1270 amino acid sequence and the following Dayhoff sequences: XLU86699_1, S49589, FIBA_PARPA, FIBB_HUMAN, P_R47189, AF004326_1, DRTENASCN_1, AF004327_1, P W01411 and FIBG BOVIN.

EXAMPLE 134: Isolation of cDNA clones Encoding Human PRO1271

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Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ[®], Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57955.

In light of an observed sequence homology between the DNA57955 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA625350, the Merck EST clone AA625350 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 297 and is herein designated as DNA66309-1538.

Clone DNA66309-1538 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 94-96 and ending at the stop codon at nucleotide positions 718-720 (Figure 297). The predicted polypeptide precursor is 208 amino acids long (Figure 298). The full-length PRO1271 protein shown in Figure 298 has an estimated molecular weight of about 21,531 daltons and a pI of about 8.99. Analysis of the full-length PRO1271 sequence shown in Figure 298 (SEQ ID NO:416) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31 and a transmembrane domain from about amino acid 166 to about amino acid 187. Clone DNA66309-1538 has been deposited with ATCC on September 15, 1998 and is assigned ATCC deposit no. 203235.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 298 (SEQ ID NO:416), evidenced significant homology between the PRO1271 amino acid sequence and the following Dayhoff sequences: S57180, S63257, AGA1_YEAST, BPU43599_1, YS8A_CAEEL, S67570, LSU54556_2, S70305, VGLX_HSVEB, and D88733 1.

EXAMPLE 135: Isolation of cDNA clones Encoding Human PRO1375

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A Merck/Wash. U. database was searched and a Merck EST was identified. This sequence was then put in a program which aligns it with other seequences from the Swiss-Prot public database, public EST databases (e.g., GenBank, Merck/Wash. U.), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the extracellular domain (ECD) protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

A consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is designated herein "DNA67003".

Based on the DNA 67003 consensus sequence, the nucleic acid (SEQ ID NO:417) was identified in a human pancreas library. DNA sequencing of the clone gave the full-length DNA sequence for PRO 1375 and the derived protein sequence for PRO 1375.

The entire coding sequence of PRO1375 is shown in Figure 299 (SEQ ID NO:417). Clone DNA67004-1614 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 104-106 and an apparent stop codon at nucleotide positions 698-700 of SEQ ID NO:417. The predicted polypeptide precursor is 198 amino acids long. The transmembrane domains are at about amino acids 11-28 (type II) and 103-125 of SEQ ID NO:418. Clone DNA67004-1614 has been deposited with ATCC and is assigned ATCC deposit no. 203115. The full-length PRO1375 protein shown in Figure 300 has an estimated molecular weight of about 22,531 daltons and a pI of about 8.47.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 300 (SEQ ID NO:418), revealed sequence identity between the PRO1375 amino acid sequence and the following Dayhoff sequences: AF026198_5, CELR12C12_5, S73465, Y011_MYCPN, S64538_1, P_P8150, MUVSHPO10_1, VSH_MUMPL and CVU59751_5.

EXAMPLE 136: Isolation of cDNA clones Encoding Human PRO1385

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57952.

In light of an observed sequence homology between the DNA57952 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3129630, the Incyte EST clone 3129630 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 301 and is herein designated as DNA68869-1610.

Clone DNA68869-1610 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 26-28 and ending at the stop codon at nucleotide positions 410-412 (Figure 301). The predicted polypeptide precursor is 128 amino acids long (Figure 302). The full-length PRO1385 protein shown in Figure 302 has an estimated molecular weight of about 13,663 daltons and a pI of about 10.97. Analysis of the full-length PRO1385 sequence shown in Figure 302 (SEQ ID NO:420) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, and glycosylaminoglycan attachment sites from about amino acid 82 to about amino acid 85 and from about amino acid 91 to about amino acid 94. Clone DNA68869-1610 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203164.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 302 (SEQ ID NO:420), evidenced low homology between the PRO1385 amino acid sequence and the following Dayhoff sequences: CELT14A8_1, LMNACHRA1_1, HXD9_HUMAN, CHKCMLF_1, HS5PP34_2, DMDRING_1, A37107_1, MMLUNGENE 1, PUM DROME and DMU25117 1.

EXAMPLE 137: Isolation of cDNA clones Encoding Human PRO1387

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Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56259.

In light of an observed sequence homology between the DNA56259 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3507924, the Incyte EST clone 3507924 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 303 and is herein designated as DNA68872-1620.

Clone DNA68872-1620 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 85-87 and ending at the stop codon at nucleotide positions 1267-1269 (Figure 303). The predicted polypeptide precursor is 394 amino acids long (Figure 304). The full-length PRO1387 protein shown in Figure 304 has an estimated molecular weight of about 44,339 daltons and a pI of about 7.10. Analysis of the full-length PRO1387 sequence shown in Figure 304 (SEQ ID NO:422) evidences the presence

of the following: a signal peptide from about amino acid 1 to about amino acid 19, a transmembrane domain from about amino acid 275 to about amino acid 296, potential N-glycosylation sites from about amino acid 76 to about amino acid 79, from about amino acid 231 to about amino acid 234, from about amino acid 302 to about amino acid 305, from about amino acid 307 to about amino acid 310 and from about amino acid 376 to about amino acid 379, and amino acid sequence blocks having homology to myelin p0 protein from about amino acid 210 to about amino acid 239 and from about amino acid 92 to about amino acid 121. Clone DNA68872-1620 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203160.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 304 (SEQ ID NO:422), evidenced significant homology between the PRO1387 amino acid sequence and the following Dayhoff sequences: P_W36955, MYP0_HETFR, HS46KDA_1, AF049498_1, MYO0_HUMAN, AF030454_1, A53268, SHPTCRA_1, P_W14146 and GEN12838.

EXAMPLE 138: Isolation of cDNA clones Encoding Human PRO1384

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA54192. Based on the DNA54192 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1384.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGCAGCCCCTGTGACACAAACTGG-3' (SEQ ID NO:425)
reverse PCR primer 5'-CTGAGATAACCGAGCCATCCTCCCAC-3' (SEQ ID NO:426)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA54192 sequence which had the following nucleotide sequence:

hybridization probe

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25 5'-GGAGATAGCTGCTATGGGTTCTTCAGGCACAACTTAACATGGGAAG-3' (SEQ ID NO:427)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1384 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1384 (designated herein as DNA71159-1617 [Figure 305, SEQ ID NO:423]; and the derived protein sequence for PRO1384.

The entire coding sequence of PRO1384 is shown in Figure 305 (SEQ ID NO:423). Clone DNA71159-1617 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 182-184 and an apparent stop codon at nucleotide positions 869-871. The predicted polypeptide precursor is 229 amino acids long. The full-length PRO1384 protein shown in Figure 306 has an estimated molecular weight of about 26,650 daltons and a pI of about 8.76. Additional features include a type II

transmembrane domain at about amino acids 32-57, and potential N-glycosylation sites at about amino acids 68-71, 120-123, and 134-137.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 306 (SEQ ID NO:424), revealed homology between the PRO1384 amino acid sequence and the following Dayhoff sequences: AF054819_1, HSAJ1687_1, AF009511_1, AB010710_1, GEN13595, HSAJ673_1, GEN13961, AB005900_1, LECH_CHICK, AF021349_1, and NK13_RAT.

Clone DNA71159-1617 has been deposited with ATCC and is assigned ATCC deposit no. 203135.

EXAMPLE 139: Use of PRO as a hybridization probe

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The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

EXAMPLE 140: Expression of PRO in E. coli

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in E. coli.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for amplicilin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected E. coli strain using the methods described in Sambrook et al., \underline{supra} . Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

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PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate 2H2O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column

using the calculated extinction coefficient based on its amino acid sequence.

using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 141: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., <u>supra</u>. The resulting vector is called pRK5-PRO.

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In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μ g pRK5-PRO DNA is mixed with about 1 μ g DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 μ l of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 μ l of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

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Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μ Ci/ml ³⁵S-cysteine and 200 μ Ci/ml ³⁵S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

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In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., <u>Proc. Natl. Acad. Sci.</u>, <u>12</u>:7575 (1981). 293 cells are grown to

maximal density in a spinner flask and 700 μ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μ g/ml bovine insulin and 0.1 μ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

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In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., <u>Current Protocols of Molecular Biology</u>, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., <u>Nucl. Acids Res.</u> 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect (Quiagen), Dosper or Fugene (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3 x 10-7 cells are frozen

in an ampule for further growth and production as described below.

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The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μ m filtered PS20 with 5% 0.2 μ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x 10⁵ cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 106 cells/mL. On day 0, the cell number pH ie determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a $0.22 \mu m$ filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 142: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding

PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 143: Expression of PRO in Baculovirus-Infected Insect Cells

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The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGoldTM virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound

protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 144: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

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Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, <u>supra</u>. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

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Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

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After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

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The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

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The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

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EXAMPLE 145: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the

art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSETM (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 146: Drug Screening

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This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is

separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

EXAMPLE 147: Rational Drug Design

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The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (i.e., a PRO polypeptide) or of small molecules with which they interact, e.g., agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide in vivo (c.f., Hodgson, Bio/Technology, 2: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda et al., J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced

peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

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EXAMPLE 148: Stimulation of Heart Neonatal Hypertrophy (Assay 1)

This assay is designed to measure the ability of PRO polypeptides to stimulate hypertrophy of neonatal heart. PRO polypeptides testing positive in this assay are expected to be useful for the therapeutic treatment of various cardiac insufficiency disorders.

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Cardiac myocytes from 1-day old Harlan Sprague Dawley rats were obtained. Cells (180 μ l at 7.5 x 10⁴/ml, serum <0.1%, freshly isolated) are added on day 1 to 96-well plates previously coated with DMEM/F12 + 4% FCS. Test samples containing the test PRO polypeptide or growth medium only (hegative control) (20 μ l/well) are added directly to the wells on day 1. PGF (20 μ l/well) is then added on day 2 at final concentration of 10⁻⁶ M. The cells are then stained on day 4 and visually scored on day 5, wherein cells showing no increase in size as compared to negative controls are scored 0.0, cells showing a small to moderate increase in size as compared to negative controls are scored 1.0 and cells showing a large increase in size as compared to negative controls are scored 1.0 and cells showing a score of 1.0 or greater.

The following polypeptides tested positive in this assay: PRO1312.

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EXAMPLE 149: Stimulation of Endothelial Cell Proliferation (Assay 8)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to stimulate adrenal cortical capillary endothelial cell (ACE) growth. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

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Bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus VEGF (5 ng/ml); and (4) ACE cells plus FGF (5ng/ml). The control or test sample, (in 100 microliter volumes), was then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO₂. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

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The activity of a PRO polypeptide was calculated as the fold increase in proliferation (as determined by the acid phosphatase activity, OD 405 nm) relative to (1) cell only background, and (2) relative to maximum stimulation by VEGF. VEGF (at 3-10 ng/ml) and FGF (at 1-5 ng/ml) were employed as an activity reference for maximum stimulation. Results of the assay were considered "positive" if the observed stimulation was ≥ 50% increase over background. VEGF (5 ng/ml) control at 1% dilution gave 1.24 fold stimulation; FGF (5 ng/ml) control at 1% dilution gave 1.46 fold stimulation.

The following PRO polypeptides tested positive in this assay: PRO1154 and PRO1186.

EXAMPLE 150: Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9)

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The ability of various PRO polypeptides to inhibit VEGF stimulated proliferation of endothelial cells was tested. Polypeptides testing positive in this assay are useful for inhibiting endothelial cell growth in mammals where such an effect would be beneficial, e.g., for inhibiting tumor growth.

Specifically, bovine adrenal cortical capillary endothelial cells (ACE) (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus 5 ng/ml FGF; (4) ACE cells plus 3 ng/ml VEGF; (5) ACE cells plus 3 ng/ml VEGF plus 1 ng/ml TGF-beta; and (6) ACE cells plus 3 ng/ml VEGF plus 5 ng/ml LIF. The test samples, poly-his tagged PRO polypeptides (in 100 microliter volumes), were then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO₂. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

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The activity of PRO polypeptides was calculated as the percent inhibition of VEGF (3 ng/ml) stimulated proliferation (as determined by measuring acid phosphatase activity at OD 405 nm) relative to the cells without stimulation. TGF-beta was employed as an activity reference at 1 ng/ml, since TGF-beta blocks 70-90% of VEGF-stimulated ACE cell proliferation. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis. Numerical values (relative inhibition) are determined by calculating the percent inhibition of VEGF stimulated proliferation by the PRO polypeptides relative to cells without stimulation and then dividing that percentage into the percent inhibition obtained by TGF- β at 1 ng/ml which is known to block 70-90% of VEGF stimulated cell proliferation. The results are considered positive if the PRO polypeptide exhibits 30% or greater inhibition of VEGF stimulation of endothelial cell growth (relative inhibition 30% or greater).

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The following polypeptide tested positive in this assay: PRO812.

EXAMPLE 151: Stimulatory Activity in Mixed Lymphocyte Reaction (MLR) Assay (Assay 24)

This example shows that certain polypeptides of the invention are active as a stimulator of the proliferation of stimulated T-lymphocytes. Compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial. A therapeutic agent may take the form of antagonists of the polypeptide of the invention, for example, murine-human chimeric, humanized or human antibodies against the polypeptide.

The basic protocol for this assay is described in Current Protocols in Immunology, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc.

More specifically, in one assay variant, peripheral blood mononuclear cells (PBMC) are isolated from mammalian individuals, for example a human volunteer, by leukopheresis (one donor will supply stimulator PBMCs, the other donor will supply responder PBMCs). If desired, the cells are frozen in fetal bovine serum and DMSO after isolation. Frozen cells may be thawed overnight in assay media (37°C, 5% CO₂) and then washed and resuspended to $3x10^6$ cells/ml of assay media (RPMI; 10% fetal bovine serum, 1% penicillin/streptomycin, 1% glutamine, 1% HEPES, 1% non-essential amino acids, 1% pyruvate). The stimulator PBMCs are prepared by irradiating the cells (about 3000 Rads).

The assay is prepared by plating in triplicate wells a mixture of:

100:1 of test sample diluted to 1% or to 0.1%,

50: l of irradiated stimulator cells, and

50: l of responder PBMC cells.

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100 microliters of cell culture media or 100 microliter of CD4-IgG is used as the control. The wells are then incubated at 37°C, 5% CO₂ for 4 days. On day 5, each well is pulsed with tritiated thymidine (1.0 mC/well; Amersham). After 6 hours the cells are washed 3 times and then the uptake of the label is evaluated.

In another variant of this assay, PBMCs are isolated from the spleens of Balb/c mice and C57B6 mice. The cells are teased from freshly harvested spleens in assay media (RPMI; 10% fetal bovine serum, 1% penicillin/streptomycin, 1% glutamine, 1% HEPES, 1% non-essential amino acids, 1% pyruvate) and the PBMCs are isolated by overlaying these cells over Lympholyte M (Organon Teknika), centrifuging at 2000 rpm for 20 minutes, collecting and washing the mononuclear cell layer in assay media and resuspending the cells to 1x10⁷ cells/ml of assay media. The assay is then conducted as described above.

Positive increases over control are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein.

The following PRO polypeptides tested positive in this assay: PRO826, PRO1068, PRO1184, PRO1346 and PRO1375.

EXAMPLE 152: Retinal Neuron Survival (Assay 52)

This example demonstrates that certain PRO polypeptides have efficacy in enhancing the survival of retinal neuron cells and, therefore, are useful for the therapeutic treatment of retinal disorders or injuries including, for example, treating sight loss in mammals due to retinitis pigmentosum, AMD, etc.

Sprague Dawley rat pups at postnatal day 7 (mixed population: glia and retinal neuronal types) are killed by decapitation following CO₂ anesthesia and the eyes are removed under sterile conditions. The neural retina is dissected away from the pigment epithelium and other ocular tissue and then dissociated into a single cell suspension using 0.25% trypsin in Ca²⁺, Mg²⁺-free PBS. The retinas are incubated at 37°C for 7-10 minutes after which the trypsin is inactivated by adding 1 ml soybean trypsin inhibitor. The cells are plated at 100,000 cells per well in 96 well plates in DMEM/F12 supplemented with N2 and with or without the specific test PRO polypeptide. Cells for all experiments are grown at 37°C in a water saturated atmosphere of 5% CO₂. After 2-3 days in culture, cells are stained with calcein AM then fixed using 4% paraformaldehyde and stained with DAPI for determination of total cell count. The total cells (fluorescent) are quantified at 20X objective magnification using CCD camera and NIH image software for MacIntosh. Fields in the well are chosen at random.

The effect of various concentration of PRO polypeptides are reported herein where percent survival is calculated by dividing the total number of calcein AM positive cells at 2-3 days in culture by the total number of DAPI-labeled cells at 2-3 days in culture. Anything above 30% survival is considered positive.

The following PRO polypeptides tested positive in this assay using polypeptide concentrations within the range of 0.01% to 1.0% in the assay: PRO828, PRO826, PRO1068 and PRO1132.

EXAMPLE 153: Rod Photoreceptor Cell Survival (Assay 56)

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This assay shows that certain polypeptides of the invention act to enhance the survival/proliferation of rod photoreceptor cells and, therefore, are useful for the therapeutic treatment of retinal disorders or injuries including, for example, treating sight loss in mammals due to retinitis pigmentosum, AMD, etc.

Sprague Dawley rat pups at 7 day postnatal (mixed population: glia and retinal neuronal cell types) are killed by decapitation following CO₂ anesthesis and the eyes are removed under sterile conditions. The neural retina is dissected away form the pigment epithelium and other ocular tissue and then dissociated into a single cell suspension using 0.25% trypsin in Ca²⁺, Mg²⁺-free PBS. The retinas are incubated at 37°C for 7-10 minutes after which the trypsin is inactivated by adding 1 ml soybean trypsin inhibitor. The cells are plated at 100,000 cells per well in 96 well plates in DMEM/F12 supplemented with N₂. Cells for all experiments are grown at 37°C in a water saturated atmosphere of 5% CO₂. After 2-3 days in culture, cells are fixed using 4% paraformaldehyde, and then stained using CellTracker Green CMFDA. Rho 4D2 (ascites or IgG 1:100), a monoclonal antibody directed towards the visual pigment rhodopsin is used to detect rod photoreceptor cells by indirect immunofluorescence. The results are calculated as % survival: total number of calcein. rhodopsin positive cells at 2-3 days in culture, divided by the total number of rhodopsin positive cells at time 2-3 days in culture. The total cells (fluorescent) are quantified at 20x objective magnification using a CCD camera and NIH image software for MacIntosh. Fields in the well are chosen at random.

The following polypeptides tested positive in this assay: PRO536, PRO943, PRO828, PRO826, PRO1068 and PRO1132.

EXAMPLE 154: Induction of c-fos in Endothelial Cells (Assay 34)

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This assay is designed to determine whether PRO polypeptides show the ability to induce c-fos in endothelial cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in growth media (50% Ham's F12 w/o GHT: low glucose, and 50% DMEM without glycine: with NaHCO3, 1% glutamine, 10 mM HEPES, 10% FBS, 10 ng/ml bFGF) were plated on 96-well microtiter plates at a cell density of 1x10⁴ cells/well. The day after plating, the cells were starved by removing the growth media and treating the cells with 100 μl/well test samples and controls (positive control = growth media; negative control = Protein 32 buffer = 10 mM HEPES, 140 mM NaCl, 4% (w/v) mannitol, pH 6.8). The cells were incubated for 30 minutes at 37°C, in 5% CO₂. The samples were removed, and the first part of the bDNA kit protocol (Chiron Diagnostics, cat. #6005-037) was followed, where each capitalized reagent/buffer listed below was available from the kit.

Briefly, the amounts of the TM Lysis Buffer and Probes needed for the tests were calculated based on information provided by the manufacturer. The appropriate amounts of thawed Probes were added to the TM Lysis Buffer. The Capture Hybridization Buffer was warmed to room temperature. The bDNA strips were set up in the metal strip holders, and $100 \mu l$ of Capture Hybridization Buffer was added to each b-DNA well needed, followed by incubation for at least 30 minutes. The test plates with the cells were removed from the incubator, and the media was gently removed using the vacuum manifold. $100 \mu l$ of Lysis Hybridization Buffer with Probes were quickly pipetted into each well of the microtiter plates. The plates were then incubated at 55°C for 15 minutes. Upon removal from the incubator, the plates were placed on the vortex mixer with the microtiter adapter head and vortexed on the #2 setting for one minute. $80 \mu l$ of the lysate was removed and added to the bDNA wells containing the Capture Hybridization Buffer, and pipetted up and down to mix. The plates were incubated at 53°C for at least 16 hours.

On the next day, the second part of the bDNA kit protocol was followed. Specifically, the plates were removed from the incubator and placed on the bench to cool for 10 minutes. The volumes of additions needed were calculated based upon information provided by the manufacturer. An Amplifier Working Solution was prepared by making a 1:100 dilution of the Amplifier Concentrate (20 fm/ μ l) in AL Hybridization Buffer. The hybridization mixture was removed from the plates and washed twice with Wash A. 50 μ l of Amplifier Working Solution was added to each well and the wells were incubated at 53°C for 30 minutes. The plates were then removed from the incubator and allowed to cool for 10 minutes. The Label Probe Working Solution was prepared by making a 1:100 dilution of Label Concentrate (40 pmoles/ μ l) in AL Hybridization Buffer. After the 10-minute cool-down period, the amplifier hybridization mixture was removed and the plates were washed twice with Wash A. 50 μ l of Label Probe Working Solution was added to each well and the wells were incubated at 53°C for 15 minutes. After cooling for 10 minutes, the Substrate was warmed to room

temperature. Upon addition of 3 μ l of Substrate Enhancer to each ml of Substrate needed for the assay, the plates were allowed to cool for 10 minutes, the label hybridization mixture was removed, and the plates were washed twice with Wash A and three times with Wash D. 50 μ l of the Substrate Solution with Enhancer was added to each well. The plates were incubated for 30 minutes at 37°C and RLU was read in an appropriate luminometer.

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The replicates were averaged and the coefficient of variation was determined. The measure of activity of the fold increase over the negative control (Protein 32/HEPES buffer described above) value was indicated by chemiluminescence units (RLU). The results are considered positive if the PRO polypeptide exhibits at least a two-fold value over the negative buffer control. Negative control = 1.00 RLU at 1.00% dilution. Positive control = 8.39 RLU at 1.00% dilution.

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The following PRO polypeptides tested positive in this assay: PRO535, PRO826, PRO819, PRO1126, PRO1160 and PRO1387.

EXAMPLE 155: Inhibitory Activity in Mixed Lymphocyte Reaction (MLR) Assay (Assay 67)

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This example shows that one or more of the polypeptides of the invention are active as inhibitors of the proliferation of stimulated T-lymphocytes. Compounds which inhibit proliferation of lymphocytes are useful therapeutically where suppression of an immune response is beneficial.

The basic protocol for this assay is described in Current Protocols in Immunology, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc.

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More specifically, in one assay variant, peripheral blood mononuclear cells (PBMC) are isolated from mammalian individuals, for example a human volunteer, by leukopheresis (one donor will supply stimulator PBMCs, the other donor will supply responder PBMCs). If desired, the cells are frozen in fetal bovine serum and DMSO after isolation. Frozen cells may be thawed overnight in assay media (37°C, 5% CO₂) and then washed and resuspended to 3×10^6 cells/ml of assay media (RPMI; 10% fetal bovine serum, 1% penicillin/streptomycin, 1% glutamine, 1% HEPES, 1% non-essential amino acids, 1% pyruvate). The stimulator PBMCs are prepared by irradiating the cells (about 3000 Rads).

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The assay is prepared by plating in triplicate wells a mixture of:

100:1 of test sample diluted to 1% or to 0.1%,

50:1 of irradiated stimulator cells, and

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50: l of responder PBMC cells.

100 microliters of cell culture media or 100 microliter of CD4-IgG is used as the control. The wells are then incubated at 37° C, 5% CO₂ for 4 days. On day 5, each well is pulsed with tritiated thymidine (1.0 mC/well; Amersham). After 6 hours the cells are washed 3 times and then the uptake of the label is evaluated.

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In another variant of this assay, PBMCs are isolated from the spleens of Balb/c mice and C57B6 mice. The cells are teased from freshly harvested spleens in assay media (RPMI; 10% fetal bovine serum, 1% penicillin/streptomycin, 1% glutamine, 1% HEPES, 1% non-essential amino acids, 1% pyruvate) and the PBMCs are isolated by overlaying these cells over Lympholyte M (Organon Teknika), centrifuging at 2000

rpm for 20 minutes, collecting and washing the mononuclear cell layer in assay media and resuspending the cells to 1×10^7 cells/ml of assay media. The assay is then conducted as described above.

Any decreases below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. However, any value less than control indicates an inhibitory effect for the test protein.

The following polypeptide tested positive in this assay: PRO1114, PRO836, PRO1159, PRO1312, PRO1192, PRO1195 and PRO1387.

EXAMPLE 156: Mouse Kidney Mesangial Cell Proliferation Assay (Assay 92)

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This assay shows that certain polypeptides of the invention act to induce proliferation of mammalian kidney mesangial cells and, therefore, are useful for treating kidney disorders associated with decreased mesangial cell function such as Berger disease or other nephropathies associated with Schönlein-Henoch purpura,

celiac disease, dermatitis herpetiformis or Crohn disease. The assay is performed as follows. On day one, mouse kidney mesangial cells are plated on a 96 well plate in growth media (3:1 mixture of Dulbecco's modified Eagle's medium and Ham's F12 medium, 95% fetal bovine serum, 5% supplemented with 14 mM HEPES) and grown overnight. On day 2, PRO polypeptides are diluted at 2 concentrations(1% and 0.1%) in serum-free medium and added to the cells. Control samples are serum-free medium alone. On day 4, 20µl of the Cell Titer 96 Aqueous one solution reagent (Progema) was added to each well and the colormetric reaction was allowed to proceed for 2 hours. The absorbance (OD) is then measured at 490 nm. A positive in the assay is anything that gives an absorbance reading which is at least 15% above the control reading.

The following polypeptide tested positive in this assay: PRO819, PRO813 and PRO1066.

EXAMPLE 157: Pericyte c-Fos Induction (Assay 93)

This assay shows that certain polypeptides of the invention act to induce the expression of c-fos in pericyte cells and, therefore, are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. Specifically, on day 1, pericytes are received from VEC Technologies and all but 5 ml of media is removed from flask. On day 2, the pericytes are trypsinized, washed, spun and then plated onto 96 well plates. On day 7, the media is removed and the pericytes are treated with $100 \mu l$ of PRO polypeptide test samples and controls (positive control = DME+5% serum +/-PDGF at 500 ng/ml; negative control = protein 32). Replicates are averaged and SD/CV are determined. Fold increase over Protein 32 (buffer control) value indicated by chemiluminescence units (RLU) luminometer reading verses frequency is plotted on a histogram. Two-fold above Protein 32 value is considered positive for the assay. ASY Matrix: Growth media = low glucose DMEM = 20% FBS + 1X pen strep + 1X fungizone. Assay Media = low glucose DMEM +5% FBS.

The following polypeptides tested positive in this assay: PRO943 and PRO819.

EXAMPLE 158: Detection of PRO Polypeptides That Affect Glucose or FFA Uptake by Primary Rat Adipocytes (Assay 94)

This assay is designed to determine whether PRO polypeptides show the ability to affect glucose or FFA uptake by adipocyte cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes or hyper- or hypo-insulinemia.

In a 96 well format, PRO polypeptides to be assayed are added to primary rat adipocytes, and allowed to incubate overnight. Samples are taken at 4 and 16 hours and assayed for glycerol, glucose and FFA uptake. After the 16 hour incubation, insulin is added to the media and allowed to incubate for 4 hours. At this time, a sample is taken and glycerol, glucose and FFA uptake is measured. Media containing insulin without the PRO polypeptide is used as a positive reference control. As the PRO polypeptide being tested may either stimulate or inhibit glucose and FFA uptake, results are scored as positive in the assay if greater than 1.5 times or less than 0.5 times the insulin control.

The following PRO polypeptides tested positive as stimulators of glucose and/or FFA uptake in this assay: PRO1114, PRO1007, PRO1066, PRO848, PRO1182, PRO1198, PRO1192, PRO1271, PRO1375 and PRO1387.

The following PRO polypeptides tested positive as inhibitors of glucose and/or FFA uptake in this assay: PRO1184, PRO1360, PRO1309, PRO1154, PRO1181, PRO1186, PRO1160 and PRO1384.

EXAMPLE 159: Chondrocyte Re-differentiation Assay (Assay 110)

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This assay shows that certain polypeptides of the invention act to induce redifferentiation of chondrocytes, therefore, are expected to be useful for the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis. The assay is performed as follows. Porcine chondrocytes are isolated by overnight collagenase digestion of articulary cartilage of metacarpophalangeal joints of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm² in Ham F-12 containing 10% FBS and 4 μ g/ml gentamycin. The culture media is changed every third day and the cells are then seeded in 96 well plates at 5,000 cells/well in 100 μ l of the same media without serum and 100 μ l of the test PRO polypeptide, 5 nM staurosporin (positive control) or medium alone (negative control) is added to give a final volume of 200 μ l/well. After 5 days of incubation at 37°C, a picture of each well is taken and the differentiation state of the chondrocytes is determined. A positive result in the assay occurs when the redifferentiation of the chondrocytes is determined to be more similar to the positive control than the negative control.

The following polypeptide tested positive in this assay: PRO1282, PRO1310, PRO619, PRO943, PRO820, PRO1080, PRO1016, PRO1007, PRO1056, PRO791, PRO1111, PRO1184, PRO1360, PRO1309, PRO1107, PRO1132, PRO1131, PRO848, PRO1181, PRO1186, PRO1159, PRO1312, PRO1192 and PRO1384.

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EXAMPLE 160: Chondrocyte Proliferation Assay (Assay 111)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce the proliferation and/or redifferentiation of chondrocytes in culture. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

metacarpophalangeal joint of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm² in Ham F-12 containing 10% FBS and 4 μ g/ml gentamycin. The culture media is changed every third day and the cells are reseeded to 25,000 cells/cm2 every five days. On day 12, the cells are seeded in 96 well plates at 5,000 cells/well in 100μ l of the same media without serum and 100μ l of either serum-free medium (negative

control), staurosporin (final concentration of 5 nM; positive control) or the test PRO polypeptide are added to give a final volume of 200 μ l/well. After 5 days at 37°C, 20 μ l of Alamar blue is added to each well and the plates are incubated for an additional 3 hours at 37°C. The fluorescence is then measured in each well (Ex:530 nm; Em: 590 nm). The fluorescence of a plate containing 200 µl of the serum-free medium is measured to obtain the background. A positive result in the assay is obtained when the fluorescence of the

Porcine chondrocytes are isolated by overnight collagenase digestion of articular cartilage of the

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PRO polypeptide treated sample is more like that of the positive control than the negative control. The following PRO polypeptides tested positive in this assay: PRO1310, PRO844, PRO1312, PRO1192 and PRO1387.

This assay shows that certain polypeptides of the invention act to induce an increase in the number

EXAMPLE 161: Induction of Pancreatic β-Cell Precursor Proliferation (Assay 117)

PCR (RTQ-PCR); wherein the marker being evaluated is a transcription factor called Pdx1.

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of pancreatic β-cell precursor cells and, therefore, are useful for treating various insulin deficient states in mammals, including diabetes mellitus. The assay is performed as follows. The assay uses a primary culture of mouse fetal pancreatic cells and the primary readout is an alteration in the expression of markers that represent either β -cell precursors or mature β -cells. Marker expression is measured by real time quantitative

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14F/1640 is RPMI1640 (Gibco) plus the following:

The pancreata are dissected from E14 embryos (CD1 mice). The pancreata are then digested with collagenase/dispase in F12/DMEM at 37°C for 40 to 60 minutes (collagenase/dispase, 1.37 mg/ml, Boehringer Mannheim, #1097113). The digestion is then neutralized with an equal volume of 5% BSA and the cells are washed once with RPMI1640. At day 1, the cells are seeded into 12-well tissue culture plates (pre-coated with laminin, 20µg/ml in PBS, Boehringer Mannheim, #124317). Cells from pancreata from 1-2 embryos are distributed per well. The culture medium for this primary cuture is 14F/1640. At day 2, the media is removed and the attached cells washed with RPMI/1640. Two mls of minimal media are added in addition to the protein to be tested. At day 4, the media is removed and RNA prepared from the cells and marker expression analyzed by real time quantitative RT-PCR. A protein is considered to be active in the assay if it increases the expression of the relevant β-cell marker as compared to untreated controls.

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group A 1:1000

group B 1:1000

recombinant human insulin 10 µg/ml

Aprotinin (50µg/ml) 1:2000 (Boehringer manheim #981532)

Bovine pituitary extract (BPE) 60µg/ml

5 Gentamycin 100 ng/ml

Group A: (in 10ml PBS)

Transferrin, 100mg (Sigma T2252)

Epidermal Growth Factor, 100µg (BRL 100004)

Triiodothyronine, 10µl of 5x10⁶ M (Sigma T5516)

10 Ethanolamine, 100μl of 10⁻¹ M (Sigma E0135)

Phosphoethalamine, 100µl of 10⁻¹ M (Sigma P0503)

Selenium, 4μ l of 10^{-1} M (Aesar #12574)

Group C: (in 10ml 100% ethanol)

Hydrocortisone, $2\mu l$ of $5X10^{-3}$ M (Sigma #H0135)

Progesterone, 100µl of 1X10⁻³ M (Sigma #P6149)

Forskolin, 500µl of 20mM (Calbiochem #344270)

Minimal media:

RPMI 1640 plus transferrin (10 μ g/ml), insulin (1 μ g/ml), gentamycin (100 ng/ml), aprotinin (50 μ g/ml) and BPE (15 μ g/ml).

20 Defined media:

RPMI 1640 plus transferrin (10 μ g/ml), insulin (1 μ g/ml), gentamycin (100 ng/ml) and aprotinin (50 μ g/ml).

The following polypeptides tested positive in this assay: PRO1310, PRO1188, PRO1131 and PRO1387.

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EXAMPLE 162: Detection of Polypeptides That Affect Glucose or FFA Uptake in Skeletal Muscle (Assay 106)

This assay is designed to determine whether PRO polypeptides show the ability to affect glucose or FFA uptake by skeletal muscle cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial including, for example, diabetes or hyper- or hypo-insulinemia.

In a 96 well format, PRO polypeptides to be assayed are added to primary rat differentiated skeletal muscle, and allowed to incubate overnight. Then fresh media with the PRO polypeptide and +/- insulin are added to the wells. The sample media is then monitored to determine glucose and FFA uptake by the skeletal muscle cells. The insulin will stimulate glucose and FFA uptake by the skeletal muscle, and insulin in media without the PRO polypeptide is used as a positive control, and a limit for scoring. As the PRO polypeptide being tested may either stimulate or inhibit glucose and FFA uptake, results are scored as positive in the assay

if greater than 1.5 times or less than 0.5 times the insulin control.

The following PRO polypeptides tested positive as either stimulators or inhibitors of glucose and/or FFA uptake in this assay: PRO358, PRO1016, PRO1007, PRO826, PRO1066, PRO1029 and PRO1309.

EXAMPLE 163: Fetal Hemoglobin Induction in an Erythroblastic Cell Line (Assay 107)

This assay is useful for screening PRO polypeptides for the ability to induce the switch from adult hemoglobin to fetal hemoglobin in an erythroblastic cell line. Molecules testing positive in this assay are expected to be useful for therapeutically treating various mammalian hemoglobin-associated disorders such as the various thalassemias. The assay is performed as follows. Erythroblastic cells are plated in standard growth medium at 1000 cells/well in a 96 well format. PRO polypeptides are added to the growth medium at a concentration of 0.2% or 2% and the cells are incubated for 5 days at 37°C. As a positive control, cells are treated with 100µM hemin and as a negative control, the cells are untreated. After 5 days, cell lysates are prepared and analyzed for the expression of gamma globin (a fetal marker). A positive in the assay is a gamma globin level at least 2-fold above the negative control.

The following polypeptides tested positive in this assay: PRO1114, PRO826, PRO1066, PRO844, PRO1192 and PRO1358.

EXAMPLE 164: Induction of Pancreatic β-Cell Precursor Differentiation (Assay 89)

This assay shows that certain polypeptides of the invention act to induce differentiation of pancreatic β -cell precursor cells into mature pancreatic β -cells and, therefore, are useful for treating various insulin deficient states in mammals, including diabetes mellitus. The assay is performed as follows. The assay uses a primary culture of mouse fetal pancreatic cells and the primary readout is an alteration in the expression of markers that represent either β -cell precursors or mature β -cells. Marker expression is measured by real time quantitative PCR (RTQ-PCR); wherein the marker being evaluated is insulin.

The pancreata are dissected from E14 embryos (CD1 mice). The pancreata are then digested with collagenase/dispase in F12/DMEM at 37°C for 40 to 60 minutes (collagenase/dispase, 1.37 mg/ml, Boehringer Mannheim, #1097113). The digestion is then neutralized with an equal volume of 5% BSA and the cells are washed once with RPMI1640. At day 1, the cells are seeded into 12-well tissue culture plates (pre-coated with laminin, 20µg/ml in PBS, Boehringer Mannheim, #124317). Cells from pancreata from 1-2 embryos are distributed per well. The culture medium for this primary cuture is 14F/1640. At day 2, the media is removed and the attached cells washed with RPMI/1640. Two mls of minimal media are added in addition to the protein to be tested. At day 4, the media is removed and RNA prepared from the cells and marker expression analyzed by real time quantitative RT-PCR. A protein is considered to be active in the assay if it increases the expression of the relevant β-cell marker as compared to untreated controls.

14F/1640 is RPMI1640 (Gibco) plus the following:

group A 1:1000

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group B 1:1000

recombinant human insulin 10 µg/ml

Aprotinin (50µg/ml) 1:2000 (Boehringer manheim #981532)

Bovine pituitary extract (BPE) 60µg/ml

Gentamycin 100 ng/ml

Group A: (in 10ml PBS)

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Transferrin, 100mg (Sigma T2252)

Epidermal Growth Factor, 100µg (BRL 100004)

Triiodothyronine, 10µl of 5x10⁻⁶ M (Sigma T5516)

Ethanolamine, 100µl of 10⁻¹ M (Sigma E0135)

Phosphoethalamine, $100\mu l$ of 10^{-1} M (Sigma P0503)

Selenium, $4\mu l$ of 10^{-1} M (Aesar #12574)

10 Group C: (in 10ml 100% ethanol)

Hydrocortisone, 2µl of 5X10⁻³ M (Sigma #H0135)

Progesterone, 100μ l of $1X10^{-3}$ M (Sigma #P6149)

Forskolin, 500µl of 20mM (Calbiochem #344270)

Minimal media:

RPMI 1640 plus transferrin (10 μ g/ml), insulin (1 μ g/ml), gentamycin (100 ng/ml), aprotinin (50 μ g/ml) and BPE (15 μ g/ml).

Defined media:

RPMI 1640 plus transferrin (10 μ g/ml), insulin (1 μ g/ml), gentamycin (100 ng/ml) and aprotinin (50 μ g/ml).

The following polypeptides were positive in this assay: PRO1188, PRO1132, PRO1131 and PRO1181.

EXAMPLE 165: Skin Vascular Permeability Assay (Assay 64)

This assay shows that certain polypeptides of the invention stimulate an immune response and induce inflammation by inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal. Compounds which stimulate an immune response are useful therapeutically where stimulation of an immune response is beneficial. This skin vascular permeability assay is conducted as follows. Hairless guinea pigs weighing 350 grams or more are anesthetized with ketamine (75-80 mg/Kg) and 5 mg/Kg xylazine intramuscularly (IM). A sample of purified polypeptide of the invention or a conditioned media test sample is injected intradermally onto the backs of the test animals with $100 \mu l$ per injection site. It is possible to have about 10-30, preferably about 16-24, injection sites per animal. One μl of Evans blue dye (1% in physiologic buffered saline) is injected intracardially. Blemishes at the injection sites are then measured (mm diameter) at 1 hr and 6 hr post injection. Animals were sacrificed at 6 hrs after injection. Each skin injection site is biopsied and fixed in formalin. The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell inflatration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is

scored as negative.

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The following polypeptide tested positive in this assay: PRO1007, PRO1358 and PRO1375.

EXAMPLE 166: Induction of Endothelial Cell Apoptosis (ELISA) (Assay 109)

The ability of PRO polypeptides to induce apoptosis in endothelial cells was tested in human venous umbilical vein endothelial cells (HUVEC, Cell Systems) using a 96-well format, in 0% serum media supplemented with 100 ng/ml VEGF, 0.1% BSA, 1X penn/strep. A positive result in this assay indicates the usefulness of the polypeptide for therapeutically treating any of a variety of conditions associated with undesired endothelial cell growth including, for example, the inhibition of tumor growth. The 96-well plates used were manufactured by Falcon (No. 3072). Coating of 96 well plates were prepared by allowing gelatinization to occur for >30 minutes with 100 μ l of 0.2% gelatin in PBS solution. The gelatin mix was aspirated thoroughly before plating HUVEC cells at a final concentration of 2 x 10⁴ cells/ml in 10% serum containing medium - 100 μ l volume per well. The cells were grown for 24 hours before adding test samples containing the PRO polypeptide of interest.

To all wells, $100 \,\mu$ l of 0% serum media (Cell Systems) complemented with $100 \,\mathrm{ng/ml}$ VEGF, 0.1% BSA, 1X penn/strep was added. Test samples containing PRO polypeptides were added in triplicate at dilutions of 1%, 0.33% and 0.11%. Wells without cells were used as a blank and wells with cells only were used as a negative control. As a positive control, 1:3 serial dilutions of $50 \,\mu$ l of a 3x stock of staurosporine were used. The cells were incubated for 24 to 35 hours prior to ELISA.

ELISA was used to determine levels of apoptosis preparing solutions according to the Boehringer Manual [Boehringer, Cell Death Detection ELISA plus, Cat No. 1 920 685]. Sample preparations: 96 well plates were spun down at 1 krpm for 10 minutes (200g); the supernatant was removed by fast inversion, placing the plate upside down on a paper towel to remove residual liquid. To each well, 200 μ l of 1X Lysis buffer was added and incubation allowed at room temperature for 30 minutes without shaking. The plates were spun down for 10 minutes at 1 krpm, and 20 μ l of the lysate (cytoplasmic fraction) was transferred into streptavidin coated MTP. 80 μ l of immunoreagent mix was added to the 20 μ l lystate in each well. The MTP was covered with adhesive foil and incubated at room tempearature for 2 hours by placing it on an orbital shaker (200 rpm). After two hours, the supernatant was removed by suction and the wells rinsed three times with 250 μ l of 1X incubation buffer per well (removed by suction). Substrate solution was added (100 μ l) into each well and incubated on an orbital shaker at room temperature at 250 rpm until color development was sufficient for a photometric analysis (approx. after 10-20 minutes). A 96 well reader was used to read the plates at 405 nm, reference wavelength, 492 nm. The levels obtained for PlN 32 (control buffer) was set to 100%. Samples with levels >130% were considered positive for induction of apoptosis.

The following PRO polypeptides tested positive in this assay: PRO844.

35 EXAMPLE 167: Guinea Pig Vascular Leak (Assay 32)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce vascular permeability. Polypeptides testing positive in this assay are expected to be useful

for the therapeutic treatment of conditions which would benefit from enhanced vascular permeability including, for example, conditions which may benefit from enhanced local immune system cell infiltration.

Hairless guinea pigs weighing 350 grams or more were anesthetized with Ketamine (75-80 mg/kg) and 5 mg/kg Xylazine intramuscularly. Test samples containing the PRO polypeptide or a physiological buffer without the test polypeptide are injected into skin on the back of the test animals with $100 \mu l$ per injection site intradermally. There were approximately 16-24 injection sites per animal. One ml of Evans blue dye (1% in PBS) is then injected intracardially. Skin vascular permeability responses to the compounds (i.e., blemishes at the injection sites of injection) are visually scored by measuring the diameter (in mm) of blue-colored leaks from the site of injection at 1, 6 and 24 hours post administration of the test materials. The mm diameter of blueness at the site of injection is observed and recorded as well as the severity of the vascular leakage. Blemishes of at least 5 mm in diameter are considered positive for the assay when testing purified proteins, being indicative of the ability to induce vascular leakage or permeability. A response greater than 7 mm diameter is considered positive for conditioned media samples. Human VEGF at $0.1 \mu g/100 \mu l$ is used as a positive control, inducing a response of 4-8 mm diameter.

The following PRO polypeptides tested positive in this assay:PRO1155.

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EXAMPLE 168: Mouse Mesengial Cell Inhibition Assay (Assay 114)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to inhibit the proliferation of mouse mesengial cells in culture. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of such diseases or conditions where inhibition of mesengial cell proliferation would be beneficial such as, for example, cystic renal dysplasia, polycystic kidney disease, or other kidney disease assoiciated with abnormal mesengial cell proliferation, renal tumors, and the like.

On day 1, mouse mesengial cells are plated on a 96 well plate in growth medium (a 3:1 mixture of Dulbecco's modified Eagle's medium and Ham's F12 medium, 95%; fetal bovine serum, 5%; supplemented with 14mM HEPES) and then are allowed to grow overnight. On day 2, the PRO polypeptide is diluted at 2 different concentrations (1%, 0.1%) in serum-free medium and is added to the cells. The negative control is growth medium without added PRO polypeptide. After the cells are allowed to incubate for 48 hours, 20 μ l of the Cell Titer 96 Aqueous one solution reagent (Promega) is added to each well and the colormetric reaction is allowed to proceed for 2 hours. The absorbance (OD) is then measured at 490 nm. A positive in the assay is an absorbance reading which is at least 10% above the negative control.

The following PRO polypeptides tested positive in this assay: PRO1192 and PRO1195.

Example 169: In Vitro Antitumor Assay (Assay 161)

The antiproliferative activity of various PRO polypeptides was determined in the investigational, disease-oriented *in vitro* anti-cancer drug discovery assay of the National Cancer Institute (NCI), using a sulforhodamine B (SRB) dye binding assay essentially as described by Skehan et al., <u>J. Natl. Cancer Inst.</u> 82:1107-1112 (1990). The 60 tumor cell lines employed in this study ("the NCI panel"), as well as conditions

for their maintenance and culture *in vitro* have been described by Monks et al., <u>J. Natl. Cancer Inst.</u> 83:757-766 (1991). The purpose of this screen is to initially evaluate the cytotoxic and/or cytostatic activity of the test compounds against different types of tumors (Monks et al., *supra*; Boyd, <u>Cancer: Princ, Pract, Oncol, Update</u> 3(10):1-12 [1989]).

Cells from approximately 60 human tumor cell lines were harvested with trypsin/EDTA (Gibco), washed once, resuspended in IMEM and their viability was determined. The cell suspensions were added by pipet (100 μ L volume) into separate 96-well microtiter plates. The cell density for the 6-day incubation was less than for the 2-day incubation to prevent overgrowth. Inoculates were allowed a preincubation period of 24 hours at 37°C for stabilization. Dilutions at twice the intended test concentration were added at time zero in 100 μ L aliquots to the microtiter plate wells (1:2 dilution). Test compounds were evaluated at five half-log dilutions (1000 to 100,000-fold). Incubations took place for two days and six days in a 5% CO₂ atmosphere and 100% humidity.

After incubation, the medium was removed and the cells were fixed in 0.1 ml of 10% trichloroacetic acid at 40°C. The plates were rinsed five times with deionized water, dried, stained for 30 minutes with 0.1 ml of 0.4% sulforhodamine B dye (Sigma) dissolved in 1% acetic acid, rinsed four times with 1% acetic acid to remove unbound dye, dried, and the stain was extracted for five minutes with 0.1 ml of 10 mM Tris base [tris(hydroxymethyl)aminomethane], pH 10.5. The absorbance (OD) of sulforhodamine B at 492 nm was measured using a computer-interfaced, 96-well microtiter plate reader.

A test sample is considered positive if it shows at least 50% growth inhibitory effect at one or more concentrations. The results are shown in the following table, where the abbreviations are as follows:

NSCL = non-small cell lung carcinoma

CNS = central nervous system

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25	Test compound	Concentration	<u>Days</u>	Tumor Cell Line Type	Cell Line Designation
	PRO1016	0.1 nM	2	Leukemia	K-568
	PRO1016	0.1 nM	2	Leukemia	MOLT-4
	PRO1016	0.1 nM	2	Leukemia	RPMI-8226
	PRO1016	0.1 nM	2	NSCL	A549/ATCC
30	PRO1016	0.1 nM	2	NSCL	EKVX
	PRO1016	0.1 nM	2	NSCL	NCI-H23
	PRO1016	0.1 nM	2	NSCL	NCI-H522
	PRO1016	0.1 nM	2	Colon	KM-12
	PRO1016	0.1 nM	2	CNS	SF-295
35	PRO1016	0.1 nM	2	Melaпоma	SK-MEL-5
	PRO1016	0.1 nM	2	Melanoma	UACC-257
	PRO1016	0.1 nM	2	Ovarian	OVCAR-3
	PRO1016	0.1 nM	2.	Ovarian	OVCAR-4
	PRO1016	0.1 nM	2	Breast	NCI/SDR-RES
40	PRO1016	0.1 nM	2	Breast	T-47D
	PRO1016	0.1 nM	6 .	Leukemia	CCRF-CEM
	PRO1016	0.1 nM	6	Leukemia	K-562

Table 7 (cont')

			Table 7 (cont')		
	Test compound	Concentration	<u>Days</u>	Tumor Cell Line Type	<u>Cell Line</u>
				•	Designation
	PRO1016	0.1 nM	6	Leukemia	MOLT-4
	PRO1016	0.1 nM	6	Leukemia	RPMI-8226
5	PRO1016	0.1 nM	6	NSCL	A549/ATCC
	PRO1016	0.1 nM	6	NSCL	EKVX
	PRO1016	0.1 nM	6	NSCL	HOP-62
	PRO1016	0.1 nM	6	NSCL	NCI-H23
	PRO1016	0.1 nM	6	NSCL	NCI-H322M
10	PRO1016	0.1 nM	6	NSCL	NCI-H460
	PRO1016	0.1 nM	6	NSCL	NCI-H522
	PRO1016	0.1 nM	6	Colon	COLO 205
	PRO1016	0.1 nM	6	Colon	CHT-116
	PRO1016	0.1 nM	6	Colon	HCT-15
15	PRO1016	0.1 nM	6	Colon	HT-29
	PRO1016	0.1 nM	6	Colon	SW-620
	PRO1016	0.1 nM	6	CNS	SF-295
	PRO1016	0.1 nM	6 .	CNS	SF-539
	PRO1016	0.1 nM	6	CNS	SNB-19
20	PRO1016	0.1 nM	6	CNS	U251
	PRO1016	0.1 nM	6	Melanoma	LOX IMVI
	PRO1016	0.1 nM	6	Melanoma	MALME-3M
	PRO1016	0.1 nM	6	Melanoma	SK-MEL-28
	PRO1016	0.1 nM	6	Melanoma	SK-MEL-5
25	PRO1016	0.1 nM	6	Melanoma	UACC-257
	PRO1016	0.1 nM	6	Melanoma	UACC-62
	PRO1016	0.1 nM	6	Ovarian	IGROV1
	PRO1016	0.1 nM	6	Ovarian	OVCAR-3
	PRO1016	0.1 nM	6	Ovarian	OVCAR-4
30	PRO1016	0.1 nM	6	Ovarian	OVCAR-8
	PRO1016	0.1 nM	6	Renal	ACHN
	PRO1016	0.1 nM	6	Renal	RXF 393
	PRO1016	0.1 nM	6	Renal	SN12C
	PRO1016	0.1 nM	6	Renal	TK-10
35	PRO1016	0.1 nM	6	Prostate	PC-3
	PRO1016	0.1 nM	6	Breast	MCF-7
	PRO1016	0.1 nM	6	Breast	NCI/ADR-RES
	PRO1016	0.1 nM	6	Breast	MDA-MB-231
	PRO1016	0.1 nM	6	Breast	MDA-MB-435
40	PRO1016	0.1 nM	6	Breast	MDA-N
	PRO1016	0.1 nM	6	Breast	BT-549
	PRO1016	0.1 nM	6	Breast	T-47D
	PRO1186	95 nM	2	NSCL	NCI-H226
	PRO1186	95 nM	2	Colon	Colo205
45	PRO1186	2.2 nM	6	Breast	MDA-N
	PRO1186	114 nM	2	NSCL	NCI-H322M
	PRO1186	114 nM	2	CNS	SF-268; SF-539
	PRO1186	114 nM	2	Ovarian	IGFOVI
	PRO1186	114 nM	2	Renal	786-0; SN12C; TK-
50					10
	PRO1186	114 nM	6	Leukemia	MOLT-4; RPMI-
					8226
	PRO1186	114 nM	6	Melanoma	LOX IMVI
	PRO1186	114 nM	6	Ovarian	OVCAR-4; SK-OV-
55					3

			Table 7 (cont	ני	
	Test compound	Concentration	<u>Days</u>	Tumor Cell Line Type	Cell Line
	_				<u>Designation</u>
	PRO1186	114 nM	6	Breast	MDA-MB-435; T-
					47D
5	PRO1186	8.1 nM	6	Leukemia	K-562
	PRO1186	8.1 nM	6	NSCL	HOP-62
	PRO1186	8.1 nM	6	Colon	Colo205; HCC-2998
	PRO1186	8.1 nM	6	Breast	T-47D
	PRO1186	15.4 nM	6	Leukemia	K-562
10	PRO1186	3.6 nM	2	Ovarian	OVCAR-3
	PRO1186	3.6 nM	6	NSCL	HOP-62

The results of these assays demonstrate that the positive testing PRO polypeptides are useful for inhibiting neoplastic growth in a number of different tumor cell types and may be used therapeutically therefor.. Antibodies against these PRO polypeptides are useful for affinity purification of these useful polypeptides. Nucleic acids encoding these PRO polypeptides are useful for the recombinant preparation of these polypeptides.

EXAMPLE 170: Gene Amplification in Tumors

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This example shows that certain PRO polypeptide-encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. Therapeutic agents may take the form of antagonists of the PRO polypeptide, for example, murine-human chimeric, humanized or human antibodies against a PRO polypeptide.

The starting material for the screen was genomic DNA isolated from a variety cancers. The DNA is quantitated precisely, e.g., fluorometrically. As a negative control, DNA was isolated from the cells of ten normal healthy individuals which was pooled and used as assay controls for the gene copy in healthy individuals (not shown). The 5' nuclease assay (for example, TaqManTM) and real-time quantitative PCR (for example, ABI Prizm 7700 Sequence Detection SystemTM (Perkin Elmer, Applied Biosystems Division, Foster City, CA)), were used to find genes potentially amplified in certain cancers. The results were used to determine whether the DNA encoding the PRO polypeptide is over-represented in any of the primary lung or colon cancers or cancer cell lines or breast cancer cell lines that were screened. The primary lung cancers were obtained from individuals with tumors of the type and stage as indicated in Table 8. An explanation of the abbreviations used for the designation of the primary tumors listed in Table 8 and the primary tumors and cell lines referred to throughout this example are given below.

The results of the TaqManTM are reported in delta (Δ) Ct units. One unit corresponds to 1 PCR cycle or approximately a 2-fold amplification relative to normal, two units corresponds to 4-fold, 3 units to 8-fold amplification and so on. Quantitation was obtained using primers and a TaqManTM fluorescent probe derived from the PRO polypeptide-encoding gene. Regions of the PRO polypeptide-encoding gene which are most likely to contain unique nucleic acid sequences and which are least likely to have spliced out introns are

preferred for the primer and probe derivation, e.g., 3'-untranslated regions. The sequences for the primers and probes (forward, reverse and probe) used for the PRO polypeptide gene amplification analysis were as follows:

PRO290 (DNA35680-1212):

35680.tm.p:

5 5'-CCACCAATGGCAGCCCCACCT-3' (SEQ ID NO:428)

35680.tm.f:

5'-GACTGCCCTCCCTGCCA-3' (SEQ ID NO:429)

35680.tm.r:

5'-CAAAAAGCCTGGAAGTCTTCAAAG-3' (SEQ ID NO:430)

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PRO341 (DNA26288-1239):

26288.tm.f1:

5'-CAGCTGGACTGCAGGTGCTA-3' (SEQ ID NO:431)

26288.tm,r1:

15 5'-CAGTGAGCACAGCAAGTGTCCT-3' (SEQ ID NO:432)

26288.tm.p1:

5'-GGCCACCTCCTTGAGTCTTCAGTTCCCT-3' (SEQ ID NO:433)

PRO535 (DNA49143-1429):

20 <u>49143.tm.fl</u>:

5'-CAACTACTGGCTAAAGCTGGTGAA-3' (SEQ ID NO:434)

49143.tm.rl:

5'-CCTTTCTGTATAGGTGATACCCAATGA-3' (SEQ ID NO:435)

49143.tm.p1:

25 5'-TGGCCATCCCTACCAGAGGCAAAA-3' (SEQ ID NO:436)

PRO619 (DNA49821-1562):

49821.tm.fl:

5'-CTGAAGACGACGCGGATTACTA-3' (SEQ ID NO:437)

30 <u>49821.tm,r1</u>:

5'-GGCAGAAATGGGAGGCAGA-3' (SEQ ID NO:438)

49821.tm.p1:

5'-TGCTCTGTTGGCTACGGCTTTAGTCCCTAG-3' (SEQ ID NO:439)

35 <u>PRO809 (DNA57836-1338)</u>:

57836.tm.f1:

5'-AGCAGCAGCCATGTAGAATGAA-3' (SEQ ID NO:440)

PCT/US00/08439 WO 00/73454 57836.tm.rl: 5'-AATACGAACAGTGCACGCTGAT-3' (SEQ ID NO:441) 57836.tm.p1: 5'-TCCAGAGAGCCAAGCACGGCAGA-3' (SEQ ID NO:442) 5 PRO830 (DNA56866-1342): 56866.tm.f1: 5'-TCTAGCCAGCTTGGCTCCAATA-3' (SEQ ID NO:443) 56866.tm.r1: 5'-CCTGGCTCTAGCACCAACTCATA-3' (SEQ ID NO:444) 10 56866.tm.p1: 5'-TCAGTGGCCCTAAGGAGATGGGCCT-3' (SEQ ID NO:445) PRO848 (DNA59839-1461): 59839.tm.fl: 15 5'-CAGGATACAGTGGGAATCTTGAGA-3' (SEQ ID NO:446) 59839.tm.r1: 5'-CCTGAAGGGCTTGGAGCTTAGT-3' (SEQ ID NO:447) 59839.tm.p1: 5'-TCTTTGGCCATTTCCCATGGCTCA-3' (SEQ ID NO:448) 20 PRO943 (DNA52192-1369): 52192.tm.f1: 5'-CCCATGGCGAGGAGGAAT-3' (SEQ ID NO:449) 52192.tm.r1: 25 5'-TGCGTACGTGTGCCTTCAG-3' (SEQ ID NO:450) 52192.tm,p1: 5'-CAGCACCCCAGGCAGTCTGTGTGT-3' (SEQ ID NO:451) PRO1005 (DNA57708-1411): 30 57708.tm.f1: 5'-AACGTGCTACACGACCAGTGTACT-3' (SEQ ID NO:452) 57708.tm.r1: 5'-CACAGCATATTCAGATGACTAAATCCA-3' (SEQ ID NO:453) 57708,tm.p1:

(SEQ ID NO:454)

5'-TTGTTTAGTTCTCCACCGTGTCTCCACAGAA-3'

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PRO1009 (DNA57129-14	{13) :
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57129.tm.fl:

5'-TGTCAGAATGCAACCTGGCTT-3' (SEQ ID NO:455)

57129.tm.rl:

5'-TGATGTGCCTGGCTCAGAAC-3' (SEQ ID NO:456)

5 <u>57129.tm.p1</u>:

5'-TGCACCTAGATGTCCCCAGCACCC-3' (SEQ ID NO:457)

PRO1097 (DNA59841-1460):

59841.tm.fl:

10 5'-AAGATGCGCCAGGCTTCTTA-3' (SEQ ID NO:458)

59841.tm.r1:

5'-CTCCTGTACGGTCTGCTCACTTAT-3' (SEQ ID NO:459)

59841.tm.p1:

5'-TGGCTGTCAGTCCAGTGTGCATGG-3' (SEQ ID NO:460)

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PRO1107 (DNA59606-1471):

59606.tm.fl:

5'-GCATAGGGATAGATAAGATCCTGCTTTAT-3' (SEQ ID NO:461)

59606.tm.r1:

20 5'-CAAATTAAAGTACCCATCAGGAGAGAA-3' (SEQ ID NO:462)

59606.tm.p1:

5'-AAGTTGCTAAATATATACATTATCTGCGCCAAGTCCA-3' (SEQ ID NO:463)

PRO1111 (DNA58721-1475):

25 58721.tm.f1:

5'-GTGCTGCCCACAATTCATGA-3' (SEQ ID NO:464)

58721.tm.r1:

5'-GTCCTTGGTATGGGTCTGAATTATAT-3' (SEQ ID NO:465

58721.tm.pl:

30 5'-ACTCTCTGCACCCCACAGTCACCACTATCTC-3' (SEQ ID NO:466)

PRO1153 (DNA59842-1502):

59842.tm.f1:

5'-CTGAGGAACCAGCCATGTCTCT-3' (SEQ ID NO:467)

35 <u>59842.tm.rl</u>:

5'-GACCAGATGCAGGTACAGGATGA-3' (SEQ ID NO:468)

59842.tm.pl;

5'-CTGCCCCTTCAGTGATGCCAACCTT-3' (SEQ ID NO:469)

PRO1182 (DNA59848-1512):

59848.tm.f1:

5 5'-GGGTGGAGGCTCACTGAGTAGA-3' (SEQ ID NO:470)

59848.tm.r1:

5'-CAATACAGGTAATGAAACTCTGCTTCTT-3' (SEQ ID NO:471)

59848.tm.p1;

5'-TCCTCTTAAGCATAGGCCATTTTCTCAGTTTAGACA-3' (SEQ ID NO:472)

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PRO1184 (DNA59220-1514):

59220.tm.f1:

5'-GGTGGTCTTGGTCTCAC-3' (SEQ ID NO:473)

59220.tm.r1;

15 5'-CCGTCGTTCAGCAACATGAC-3' (SEQ ID NO:474)

59220.tm.p1;

5'-ACCGCCTACCGCTGTGCCCA-3' (SEQ ID NO:475)

PRO1187 (DNA62876-1517):

20 <u>62876,tm.fl:</u>

5'-CAGTAAAACCACAGGCTGGATTT-3' (SEQ ID NO:476)

62876.tm.r1:

5'-CCTGAGAGCAAGAAGGTTGAGAAT-3' (SEQ ID NO:477)

62876.tm.p1:

25 5'-TAGACAGGGACCATGGCCCGCA-3' (SEQ ID NO:478)

PRO1281 (DNA59820-1549):

59820.tm.fl:

5'-TGGGCTGTAGAAGAGTTGTTG-3' (SEQ ID NO:479)

30 <u>59820.tm.r1</u>:

5'-TCCACACTTGGCCAGTTTAT-3' (SEQ ID NO:480)

59820.tm.p1;

5'-CCCAACTTCTCCCTTTTGGACCCT-3' (SEQ ID NO:481)

35 PRO1112 (DNA57702-1476):

57702.tm.f1

5'-GTCCCTTCACTGTTTAGAGCATGA-3' (SEQ ID NO:482)

57702.tm.pl

5'-ACTCTCCCCTCAACAGCCTCCTGAG-3' (SEQ ID NO:483)

57702,tm,rl

5'-GTGGTCAGGGCAGATCCTTT-3' (SEQ ID NO:484)

5 PRO1185 (DNA62881-1515):

62881.tm.f1:

5'-ACAGATCCAGGAGAGACTCCACA -3' (SEQ ID NO:485)

62881.tm.p1;

5'-AGCGGCGCTCCCAGCCTGAAT -3' (SEQ ID NO:486)

10 <u>62881.tm.r1</u>:

5'-CATGATTGGTCCTCAGTTCCATC -3' (SEQ ID NO:487)

PRO1245 (DNA64884-1527):

64884.tm.f1;

15 5'-ATAGAGGGCTCCCAGAAGTG -3' (SEQ ID NO:488)

64884.tm.p1:

5'-CAGGGCCTTCAGGGCCTTCAC-3' (SEQ ID NO:489)

64884.tm.r1:

5'-GCTCAGCCAAACACTGTCA-3' (SEQ ID NO:490)

20 <u>64884.tm.f2:</u>

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5'-GGGGCCCTGACAGTGTT -3' (SEQ ID NO:491)

64884.tm.p2:

5'-CTGAGCCGAGACTGGAGCATCTACAC-3' (SEQ ID NO:492)

64884.tm.r2:

25 5'-GTGGGCAGCGTCTTGTC-3' (SEQ ID NO:493)

The 5' nuclease assay reaction is a fluorescent PCR-based technique which makes use of the 5' exonuclease activity of Taq DNA polymerase enzyme to monitor amplification in real time. Two oligonucleotide primers (forward [.f] and reverse [.r]) are used to generate an amplicon typical of a PCR reaction. A third oligonucleotide, or probe (.p), is designed to detect nucleotide sequence located between the two PCR primers. The probe is non-extendible by Taq DNA polymerase enzyme, and is labeled with a reporter fluorescent dye and a quencher fluorescent dye. Any laser-induced emission from the reporter dye is quenched by the quenching dye when the two dyes are located close together as they are on the probe. During the amplification reaction, the Taq DNA polymerase enzyme cleaves the probe in a template-dependent manner. The resultant probe fragments disassociate in solution, and signal from the released reporter dye is free from the quenching effect of the second fluorophore. One molecule of reporter dye is liberated for each new molecule synthesized, and detection of the unquenched reporter dye provides the basis for quantitative interpretation of the data.

The 5' nuclease procedure is run on a real-time quantitative PCR device such as the ABI Prism 7700TM Sequence Detection. The system consists of a thermocycler, laser, charge-coupled device (CCD) camera and computer. The system amplifies samples in a 96-well format on a thermocycler. During amplification, laser-induced fluorescent signal is collected in real-time through fiber optics cables for all 96 wells, and detected at the CCD. The system includes software for running the instrument and for analyzing the data.

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5' Nuclease assay data are initially expressed as Ct, or the threshold cycle. This is defined as the cycle at which the reporter signal accumulates above the background level of fluorescence. The Δ Ct values are used as quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results.

Table 8 describes the stage, T stage and N stage of various primary tumors which were used to screen the PRO polypeptide compounds of the invention.

Table 8
Primary Lung and Colon Tumor Profiles

	Primary Tumor Stage	Stage	Other Stage	Dukes Stag	e T Stage	N Stage
	Human lung tumor AdenoCa (SRCC724) [LT1]	IIA			T1	N1
5	Human lung tumor SqCCa (SRCC725) [LT1a]	IIB			T3	NO
	Human lung tumor AdenoCa (SRCC726) [LT2]	IB			T2	N0
	Human lung tumor AdenoCa (SRCC727) [LT3]	IIIA			T1	N2
	Human lung tumor AdenoCa (SRCC728) [LT4]	IB			T2	NO
	Human lung tumor SqCCa (SRCC729) [LT6]	IB			T2	N0
10	Human lung tumor Aden/SqCCa (SRCC730) [LT7] IA			T 1	N0
	Human lung tumor AdenoCa (SRCC731) [LT9]	IB			T2	NO
	Human lung tumor SqCCa (SRCC732) [LT10]	IIB			T2	N1
	Human lung tumor SqCCa (SRCC733) [LT11]	IIA			T1	NI
	Human lung tumor AdenoCa (SRCC734) [LT12]	IV			T2	N0
15	Human lung tumor AdenoSqCCa (SRCC735)[LT13	3]IB			T2	N0
	Human lung tumor SqCCa (SRCC736) [LT15]	ΙB			T2	N0
	Human lung tumor SqCCa (SRCC737) [LT16]	IB			T2	NO
	Human lung tumor SqCCa (SRCC738) [LT17]	IIB			T2	NI
	Human lung tumor SqCCa (SRCC739) [LT18]	IB			T2	N0
20	Human lung tumor SqCCa (SRCC740) [LT19]	IΒ			T2	N0
	Human lung tumor LCCa (SRCC741) [LT21]	IIB		•	T3	N1
	Human lung AdenoCa (SRCC811) [LT22]	1A			Tl	N0
	Human colon AdenoCa (SRCC742) [CT2]		M1	D	pT4	N0
	Human colon AdenoCa (SRCC743) [CT3]			В	pT3	N0
25	Human colon AdenoCa (SRCC744) [CT8]			В	T3	N0
	Human colon AdenoCa (SRCC745) [CT10]			Α	pT2	N0
	Human colon AdenoCa (SRCC746) [CT12]		MO, R1	В	T3	N0
	Human colon AdenoCa (SRCC747) [CT14]		pMO, RO	В	pT3	pN0
	Human colon AdenoCa (SRCC748) [CT15]		M1, R2	D	T4	N2
30	Human colon AdenoCa (SRCC749) [CT16]		pMO	В	pT3	pN0
	Human colon AdenoCa (SRCC750) [CT17]			C1	pT3	pN1
	Human colon AdenoCa (SRCC751) [CT1]		MO, R1	В	pT3	N0
	Human colon AdenoCa (SRCC752) [CT4]			В	pT3	M0
	Human colon AdenoCa (SRCC753) [CT5]		G2	Cl	pT3	pN0
35	Human colon AdenoCa (SRCC754) [CT6]		pMO, RO	В	pT3	pN0
	Human colon AdenoCa (SRCC755) [CT7]		G1	Α	pT2	pN0
	Human colon AdenoCa (SRCC756) [CT9]		G3	D	pT4	pN2
	Human colon AdenoCa (SRCC757) [CT11]			В	T3	N0
	Human colon AdenoCa (SRCC758) [CT18]		MO, RO	В	pT3	pN0
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DNA Preparation:

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DNA was prepared from cultured cell lines, primary tumors, normal human blood. The isolation was performed using purification kit, buffer set and protease and all from Quiagen, according to the manufacturer's instructions and the description below.

Cell culture lysis:

Cells were washed and trypsinized at a concentration of 7.5×10^8 per tip and pelleted by centrifuging at 1000 rpm for 5 minutes at 4°C, followed by washing again with 1/2 volume of PBS recentrifugation. The pellets were washed a third time, the suspended cells collected and washed 2x with PBS. The cells were then suspended into 10 ml PBS. Buffer C1 was equilibrated at 4°C. Qiagen protease #19155 was diluted into 6.25 ml cold ddH₂0 to a final concentration of 20 mg/ml and equilibrated at 4°C. 10 ml of G2 Buffer was prepared

by diluting Qiagen RNAse A stock (100 mg/ml) to a final concentration of 200 μ g/ml.

Buffer C1 (10 ml, 4°C) and ddH2O (40 ml, 4°C) were then added to the 10 ml of cell suspension, mixed by inverting and incubated on ice for 10 minutes. The cell nuclei were pelleted by centrifuging in a Beckman swinging bucket rotor at 2500 rpm at 4°C for 15 minutes. The supernatant was discarded and the nuclei were suspended with a vortex into 2 ml Buffer C1 (at 4°C) and 6 ml ddH₂O, followed by a second 4°C centrifugation at 2500 rpm for 15 minutes. The nuclei were then resuspended into the residual buffer using 200 μ l per tip. G2 buffer (10 ml) was added to the suspended nuclei while gentle vortexing was applied. Upon completion of buffer addition, vigorous vortexing was applied for 30 seconds. Quiagen protease (200 μ l, prepared as indicated above) was added and incubated at 50°C for 60 minutes. The incubation and centrifugation was repeated until the lysates were clear (e.g., incubating additional 30-60 minutes, pelleting at 3000 x g for 10 min., 4°C).

Solid human tumor sample preparation and lysis:

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Tumor samples were weighed and placed into 50 ml conical tubes and held on ice. Processing was limited to no more than 250 mg tissue per preparation (1 tip/preparation). The protease solution was freshly prepared by diluting into 6.25 ml cold ddH₂O to a final concentration of 20 mg/ml and stored at 4°C. G2 buffer (20 ml) was prepared by diluting DNAse A to a final concentration of 200 mg/ml (from 100 mg/ml stock). The tumor tissue was homogenated in 19 ml G2 buffer for 60 seconds using the large tip of the polytron in a laminar-flow TC hood in order to avoid inhalation of aerosols, and held at room temperature. Between samples, the polytron was cleaned by spinning at 2 x 30 seconds each in 2L ddH₂O, followed by G2 buffer (50 ml). If tissue was still present on the generator tip, the apparatus was disassembled and cleaned.

Quiagen protease (prepared as indicated above, 1.0 ml) was added, followed by vortexing and incubation at 50°C for 3 hours. The incubation and centrifugation was repeated until the lysates were clear (e.g., incubating additional 30-60 minutes, pelleting at 3000 x g for 10 min., 4°C).

Human blood preparation and lysis:

Blood was drawn from healthy volunteers using standard infectious agent protocols and citrated into 10 ml samples per tip. Quiagen protease was freshly prepared by dilution into 6.25 ml cold ddH₂O to a final concentration of 20 mg/ml and stored at 4°C. G2 buffer was prepared by diluting RNAse A to a final concentration of 200 μ g/ml from 100 mg/ml stock. The blood (10 ml) was placed into a 50 ml conical tube and 10 ml C1 buffer and 30 ml ddH₂O (both previously equilibrated to 4°C) were added, and the components mixed by inverting and held on ice for 10 minutes. The nuclei were pelleted with a Beckman swinging bucket rotor at 2500 rpm, 4°C for 15 minutes and the supernatant discarded. With a vortex, the nuclei were suspended into 2 ml C1 buffer (4°C) and 6 ml ddH₂O (4°C). Vortexing was repeated until the pellet was white. The nuclei were then suspended into the residual buffer using a 200 μ l tip. G2 buffer (10 ml) were added to the suspended nuclei while gently vortexing, followed by vigorous vortexing for 30 seconds. Quiagen protease was added (200 μ l) and incubated at 50°C for 60 minutes. The incubation and centrifugation was repeated until the lysates were clear (e.g., incubating additional 30-60 minutes, pelleting at 3000 x g for 10 min., 4°C).

Purification of cleared lysates:

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(1) Isolation of genomic DNA:

Genomic DNA was equilibrated (1 sample per maxi tip preparation) with 10 ml QBT buffer. QF elution buffer was equilibrated at 50°C. The samples were vortexed for 30 seconds, then loaded onto equilibrated tips and drained by gravity. The tips were washed with 2 x 15 ml QC buffer. The DNA was eluted into 30 ml silanized, autoclaved 30 ml Corex tubes with 15 ml QF buffer (50°C). Isopropanol (10.5 ml) was added to each sample, the tubes covered with parafin and mixed by repeated inversion until the DNA precipitated. Samples were pelleted by centrifugation in the SS-34 rotor at 15,000 rpm for 10 minutes at 4°C. The pellet location was marked, the supernatant discarded, and 10 ml 70% ethanol (4°C) was added. Samples were pelleted again by centrifugation on the SS-34 rotor at 10,000 rpm for 10 minutes at 4°C. The pellet location was marked and the supernatant discarded. The tubes were then placed on their side in a drying rack and dried 10 minutes at 37°C, taking care not to overdry the samples.

After drying, the pellets were dissolved into 1.0 ml TE (pH 8.5) and placed at 50°C for 1-2 hours. Samples were held overnight at 4°C as dissolution continued. The DNA solution was then transferred to 1.5 ml tubes with a 26 gauge needle on a tuberculin syringe. The transfer was repeated 5x in order to shear the DNA. Samples were then placed at 50°C for 1-2 hours.

(2) Quantitation of genomic DNA and preparation for gene amplification assay:

The DNA levels in each tube were quantified by standard A_{260} , A_{280} spectrophotometry on a 1:20 dilution (5 μ l DNA + 95 μ l ddH₂O) using the 0.1 ml quartz cuvetts in the Beckman DU640 spectrophotometer. A_{260}/A_{280} ratios were in the range of 1.8-1.9. Each DNA samples was then diluted further to approximately 200 ng/ml in TE (pH 8.5). If the original material was highly concentrated (about 700 ng/ μ l), the material was placed at 50°C for several hours until resuspended.

Fluorometric DNA quantitation was then performed on the diluted material (20-600 ng/ml) using the manufacturer's guidelines as modified below. This was accomplished by allowing a Hoeffer DyNA Quant 200 fluorometer to warm-up for about 15 minutes. The Hoechst dye working solution (#H33258, $10 \mu l$, prepared within 12 hours of use) was diluted into 100 ml 1 x TNE buffer. A 2 ml cuvette was filled with the fluorometer solution, placed into the machine, and the machine was zeroed. pGEM 3Zf(+) (2 μl , lot #360851026) was added to 2 ml of fluorometer solution and calibrated at 200 units. An additional 2 μl of pGEM 3Zf(+) DNA was then tested and the reading confirmed at 400 +/- 10 units. Each sample was then read at least in triplicate. When 3 samples were found to be within 10% of each other, their average was taken and this value was used as the quantification value.

The fluorometricly determined concentration was then used to dilute each sample to $10 \text{ ng/}\mu\text{l}$ in ddH₂O. This was done simultaneously on all template samples for a single TaqMan plate assay, and with enough material to run 500-1000 assays. The samples were tested in triplicate with TaqmanTM primers and probe both B-actin and GAPDH on a single plate with normal human DNA and no-template controls. The diluted samples were used provided that the CT value of normal human DNA subtracted from test DNA was +/- 1 Ct. The diluted, lot-qualified genomic DNA was stored in 1.0 ml aliquots at -80°C. Aliquots which were subsequently to be used in the gene amplification assay were stored at 4°C. Each 1 ml aliquot is enough

for 8-9 plates or 64 tests.

Gene amplification assay:

The PRO polypeptide compounds of the invention were screened in the following primary tumors and the resulting Δ Ct values greater than or equal to 1.0 are reported in Tables 9A-C below.

Table 9A

			ACt valu	<u>ACt values in lung and colon primary tumors and cell line models</u>	on primary tumor	s and cell line mo	<u>sdels</u>	
Primary	Primary PRO290	PR0341	PRO535	PR0619	PRO1112	PRO809	PRO830	PRO848
Tumor								
LT-1a	1	ı	1	ı	1	ı	1.13	
LT3	ı	1	1	1.04	1	i	1	i
				1.68				
LT7	1.	t	1	1.21	1	1	ı	į
	•			1.34				
LIS	1	1	1	1.19	ı	1	1	ì
				1.34				
LT10	1	1	1	1.41	1.135	1	ı	ŀ
				2.02				
LTII	1.63	ı	1.40	1.69	1.525	1.40	1.25	2.8
				1.57				
LT12	!	ŀ	i	1.81	1.195	1.61	1.35	1.22
LT13	1.47	!	1.37	2.13	1.635	1.03	!	i
				1.74				
LT15	1.67		ı	2.08	1.775	i		1
				1.52				
LT16	Į.	1.12	ł	1	i	!	ı	i
LT17	1.22	1.33	1.42	1.83	1.455	1.10	1.17	i
				1.67				
LT18	i	i	•	1.32	1.255	!	:	1
				1.14				
LT19	2.07	ı	i	2.33	i	ŀ	1.31	i
			•	1.90				
LTZI	!	1.15	:	1.15	i	1.05	i	1.07
				1.09				
22	1.56	!	i	1.22	2.265	•	1	ŀ

Table 9A (cont')

			<u>∆Ct valu</u>	ACt values in lung and colon primary tumors and cell line models	lon primary tumo	rs and cell line m	<u>iodels</u>	
Primary	Primary PRO290	PRO341	PRO535	PR0619	PRO1112	PRO809	PRO830	PR0848
Tumor								
<u></u>	ł	ļ	1.28	1.49	:	1	1	1
8	!	. 1	ı	i	1.065	ļ	1	į
CT10	ı	ı	1.34	i	1.575	i	ı	1
CT12	ı	ı	!	!	1.315	ł	1	i
CT14	ı	ŀ	1.29	i	1.895	ì	1	į
CT15	!	ı	1.10	1.00	1.465	i	:	1
CT16	ı	i	1.35	1.02	1.255	!	:	ŀ
CT17	!	1	1.26	1.23	ı	1	!	1
ដ	ı	1	ł	1.12	1.245	i	1	ı
77	ı	!	1.03	1.25	1.535	ţ	i	!
cj.	ı	ı	i	1.34	1.975	!	ı	ı
CT6	ı	l	1.00	1.06	1.575	i	į	i
CTII	1.16	ı	1.25	1.80	2.285	i	!	1

Table 9B ACt values in lung and colon primary tumors and cell line models

,									
Prumary	PRO943	PRO1005	PRO1009	PRO1185	PRO1245 PRO1097 PRO1107 PRO1111	PRO1097	PRO1107		PRO1153
Tumor									
LT-1	ı	1.07	1	1	!	ı			1
LT-1a	ŀ	3.87	1	1	1	ŀ	ı	1	1
112	i	!		ı	ı	1.23	ŀ		ı
LT3	!	1.61	i	1.01	!	1	!		i
LT4	ł	!	l	!	1		ı		1.01
LT6	i	1.29	1	!	i		ŀ		i
LTJ	i	ı	ı	ı	i		ı		1.52
LT9	I	2.50	ı	ı	ŀ		i		i
LT10	ı	ļ	1	1	1		;		i
LTII	2.06	i	1	i	ı		1		i
LT12	2 .1	1.21	1	1	1		!		!
LT13	1.64	2.30	ı	ı	3.84		3.55		ı
	1.27								
LTIS	2.05	1.03	ı	1	1.01	!	2.47	ı	i
LT16	1	1.05	1	1	1.98		2.45		i
LT17	1.93	i	i	!	i		ı		i
LT19	2.90	i	1	1	ı	ı	i		!
LT26	ı	i	i	1.66	i	i	i		
LT30	ı	į	ı	1.58	ł		į		!
CL CL	1.92	i	2.00	1.73	1	ı	4.75	i	i
	1.70								
g G	ı	i	1.75	1		i	1.52	ŀ	1
ئ	1.37	i	1.29	ı	1	1	ı	1	ļ
	1.12								

Table 9B (cont')

<u>ACt values in lung and colon primary tumors and cell line models</u>

PRO1009 PRO1185 PRO1245 PRO1097 PRO1107 PRO1111 PRO1153	!		•		:	ı	!	!	1	1		1		16	41			
PRO1107 PR	2.82		:	1.54	:	:	1	1.57	1.59	!		!			1.1		- 1.0	
PRO1097			I	1.08	ı	1.11	1.34	ı	ı	ł				ı	ı		ı	
PR01245			ı	I	1.00	ı	ı	!	ı	ı		ı		ı	ı		ı	
PR01185			1	ı	i	ı	ŀ	ı	ı	!		i		ı	ı		1	
PRO1009	1.73		1.92	2.10	2.02	1.56	1.76	!	1.06	1.43		1		ı	1.83		ı	
Primary PRO943 PRO1005	1			1														
PRO943	2.13	1.67	1.43	1.46	i	!	1.30	1.36	!	1.88	2.51	1.41	1.75	i	2.80	2.61	1.30	
Primary Tumor	CT 10		CT12 1.43	CT14	CT15	CT16	CT17	ដ	77	CT3		CT6		G G	G G		CT18	

Table 9C

<u>ACt values in lung and colon primary tumors and cell line models</u>

5	Primary Tumor	PRO1182	PRO1184	PRO1187	PRO1281
	LT-1	1.81			
	LT-1a		1.14		
			1.09		
	LT4	1.43	1.37		
10			1.18		
•	LT6		1.78		
			1.66		
			1.05		
	LT9	1.43			
15	LT12		2.47	1.17	
			2.61		
			1.80		
	LT15	***		1.55	
20	LT16		1.01	1.33	
	LT17		-		
	LT18		1.07		
			1.13		
	LT19	_	. 1.19		
25			1.35		
			1.02		
	LT21		1.00		
			1.20		
	CL3				1.15
30	CT12		•••		1.07

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Because amplification of the various DNAs described above occurs in various cancerous numors and numor cell lines derived from various human tissues, these molecules likely play a significant role in numor formation and/or growth. As a result, amplification and/or enhanced expression of these molecules can serve as a diagnostic for detecting the presence of numor in an individual and antagonists (e.g., antibodies) directed against the proteins encoded by the above described DNA molecules would be expected to have utility in cancer therapy.

EXAMPLE 171: Identification of Receptor/Ligand Interactions

In this assay, various PRO polypeptides are tested for ability to bind to a panel of potential receptor molecules for the purpose of identifying receptor/ligand interactions. The identification of a ligand for a known receptor, a receptor for a known ligand or a novel receptor/ligand pair is useful for a variety of indications including, for example, targeting bioactive molecules (linked to the ligand or receptor) to a cell known to express the receptor or ligand, use of the receptor or ligand as a reagent to detect the presence of the ligand or receptor in a composition suspected of containing the same, wherein the composition may comprise cells suspected of expressing the ligand or receptor, modulating the growth of or another biological or immunological activity of a cell known to express or respond to the receptor or ligand, modulating the immune response of cells or toward cells that express the receptor or ligand, allowing the preparaion of agonists, antagonists and/or antibodies directed against the receptor or ligand which will modulate the growth of or a biological or immunological activity of a cell expressing the receptor or ligand, and various other indications which will be readily apparent to the ordinarily skilled artisan.

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The assay is performed as follows. A PRO polypeptide of the present invention suspected of being a ligand for a receptor is expressed as a fusion protein containing the Fc domain of human IgG (an immunoadhesin). Receptor-ligand binding is detected by allowing interaction of the immunoadhesin polypeptide with cells (e.g. Cos cells) expressing candidate PRO polypeptide receptors and visualization of bound immunoadhesin with fluorescent reagents directed toward the Fc fusion domain and examination by microscope. Cells expressing candidate receptors are produced by transient transfection, in parallel, of defined subsets of a library of cDNA expression vectors encoding PRO polypeptides that may function as receptor molecules. Cells are then incubated for 1 hour in the presence of the PRO polypeptide immunoadhesin being tested for possible receptor binding. The cells are then washed and fixed with paraformaldehyde. The cells are then incubated with fluorescent conjugated antibody directed against the Fc portion of the PRO polypeptide immunoadhesin (e.g. FITC conjugated goat anti-human-Fc antibody). The cells are then washed again and examined by microscope. A positive interaction is judged by the presence of fluorescent labeling of cells transfected with cDNA encoding a particular PRO polypeptide receptor or pool of receptors and an absence of similar fluorescent labeling of similarly prepared cells that have been transfected with other cDNA or pools of cDNA. If a defined pool of cDNA expression vectors is judged to be positive for interaction with a PRO polypeptide immunoadhesin, the individual cDNA species that comprise the pool are tested individually (the pool is "broken down") to determine the specific cDNA that encodes a receptor able to interact with the PRO polypeptide immunoadhesin.

In another embodiment of this assay, an epitope-tagged potential ligand PRO polypeptide (e.g. 8 histidine "His" tag) is allowed to interact with a panel of potential receptor PRO polypeptide molecules that have been expressed as fusions with the Fc domain of human IgG (immunoadhesins). Following a 1 hour co-incubation with the epitope tagged PRO polypeptide, the candidate receptors are each immunoprecipitated with protein A beads and the beads are washed. Potential ligand interaction is determined by western blot analysis of the immunoprecipitated complexes with antibody directed towards the epitope tag. An interaction is judged to occur if a band of the anticipated molecular weight of the epitope tagged protein is observed in the western blot analysis with a candidate receptor, but is not observed to occur with the other members of the panel of potential receptors.

Using these assays, the following receptor/ligand interactions have been herein identified:

- 10 (1) PRO943 binds to FHF1, PRO183 (FHF2), PRO184 (FHF3) and PRO185 (FHF4) and vice versa.
 - (2) PRO331 binds to PRO1133 and vice versa.

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- (3) PRO363 binds to PRO1387 and vice versa.
- (4) PRO5723 binds to PRO1387 and vice versa.
- (5) PRO1114 binds to PRO3301 and PRO9940 and vice versa.
- PRO9828 appears to be a novel fibroblast growth factor receptor (FGFR) ligand in that it binds to the known FGF receptors FGFR1, FGFR2IIIC, FGFR3IIIC and FGFR4. PRO9828 and agonists, therefore, will find use for activating the biological activities normally activated by FGF molecules including, for example, cell growth and proliferation. Antagonists of PRO9828 will find use in blocking the biological activities mediated through the FGF receptor.
- 20 (7) PRO1181 binds to PRO7170, PRO361 and PRO846.

EXAMPLE 172: Tissue Expression Distribution

Oligonucleotide probes were constructed from the PRO polypeptide-encoding nucleotide sequences shown in the figures for use in quantitative PCR amplification reactions. The oligonucleotide probes were chosen so as to give an approximately 200-600 base pair amplified fragment from the 3' end of its associated template in a standard PCR reaction. The oligonucleotide probes were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human adult and/or fetal tissue sources and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acids in the various tissues tested. Knowledge of the expression pattern or the differential expression of the PRO polypeptide-encoding nucleic acids in various different human tissue types provides a diagnostic marker useful for tissue typing, with or without other tissue-specific markers, for determining the primary tissue source of a metastatic tumor, disease diagnosis, and the like. These assays provided the following results.

	DNA Molecule	lissues w/ Significant Expression	lissues w/o Significant Expression
35	DNA16422-1209	substantia nigra, dendrocytes, uterus	hippocampus
	DNA16435-1208	substantia nigra, dendrocytes, uterus	hippocampus
	DNA26843-1389	dendrocytes, heart, uterus, colon tumor	hippocampus, substantia nigra,
			cartilage

	DNIA NASILA N	m'	Times / Cincipant Francisco
	DNA Molecule	Tissues w/ Significant Expression	Tissues w/o Significant Expression
	DNA26844-1394	HUVEC, dendrocytes, cartilage	substantia nigra, hippocampus, uterus,
	DNIA 40621 1440		prostate
	DNA40621-1440 DNA44161-1434	prostate, uterus, colon tumor	brain, heart, HUVEC, cartilage
5	DNA44101-1454	colon tumor, dendrocytes	substantia nigra, hippocampus, prostate, uterus
3	DNIA 44604 1600	dandanasta. Nanasanas manatas	
	DNA44694-1500	dendrocytes, hippocampus, prostate	colon tumor, substantia nigra, heart
	DNA48320-1433 DNA49647-1398	prostate, uterus	colon tumor, brain, heart, cartilage
	DNA53913-1490	brain, heart, prostate, uterus hippocampus	cartilage substantia nigra, dendrocytes
10	DNA53978-1443		— ·
10	DNA53976-1443 DNA53996-1442	dendrocytes, uterus, prostate	substantia nigra, colon tumor substantia nigra, heart
	DNA56050-1455	spleen, prostate, uterus, hippocampus	heart, colon tumor, dendrocytes
	DNA56110-1437	prostate, uterus, cartilage, hippocampus	heart
	DNA56410-1414	spleen, colon tumor, brain, prostate	hippocampus, substantia nigra, heart
15	DNA56436-1448	uterus, dendrocytes	
1.5	DNA56855-1447	substantia nigra, prostate, hippocampus	dendrocytes, heart, HUVEC
	DNA56860-1510	prostate, uterus colon tumor	brain, cartilage, heart, colon tumor prostate, uterus, dendrocytes
	DNA56868-1478	colon tumor, prostate	uterus, brain, heart, cartilage
	DNA56869-1545	• •	
20	DNA57699-1412	prostate, uterus, cartilage dendrocytes, hippocampus, prostate	brain, colon tumor, spleen, heart
20	DNA57704-1452		sunstantia nigra, heart colon tumor
	DNA57710-1451	brain, heart, spleen, uterus, prostate dendrocytes, hippocampus, spleen, uterus	
	DNA57711-1501	dendrocytes, hippocampus, spieen, derus dendrocytes, hippocampus, heart, cartilage	<u> </u>
	DNA57827-1493	colon tumor, hippocampus, prostate	sunstantia nigra, dendrocytes, uterus
25	DNA58723-1588	substantia nigra, cartilage uterus	hippocampus, dendrocytes, HUVEC
23	DNA58743-1609	brain, prostate, uterus	colon tumor, heart, spleen, cartilage
	DNA58846-1409	hippocampus, dendrocytes	substantia nigra, uterus, prostate,
	DI4A36040-1409	inplocatipus, delidrocytes	colon tumor
	DNA58849-1494	prostate	brain, uterus, cartilage, heart, colon
30	DNA30043-1434	prostate	tumor
	. DNA58850-1495	spleen, prostate, dendrocytes	hippocampus, substantia nigra, colon
	. DIANGOOO-1495	spicen, prostate, dendrocytes	tumor
	DNA59213-1487	spleen, cartilage, prostate, substantia nigra	
	DNA59497-1496	dendrocytes, prostate, uterus, heart	cartilage, hippocampus, substantia
35	2111137177 1170	dendrocytes, prostate, atoras, near	nigra
00	DNA59605-1418	dendrocytes, prostate, uterus	hippocampus, substantia nigra, colon
	211133003 1410	dendrocytes, prostate, atorus	tumor
	DNA59609-1470	dendrocytes	substantia nigra, hippocampus, heart,
	211125005 1170		prostate, uterus, spleen
40	DNA59612-1466	prostate, dendrocytes	hippocampus, substantia nigra, uterus,
			colon tumor
	DNA59616-1465	dendrocytes, substantia nigra, colon tumor	
	DNA59619-1464	dendrocytes, substantia nigra, colon tumor	
	DNA59625-1498	brain, colon tumor, prostate, uterus	THP-1 macrophages
45	DNA59827-1426	substantia nigra, prostate, uterus	hippocampus, dendrocytes, heart
	DNA59828-1608	dendrocytes, substantia nigra, colon tumor	••
	DNA59853-1505	prostate	brain, uterus, spleen, heart, colon
		F	tumor
	DNA59854-1459	cartilage	prostate, brain, heart, colon tumor
50	DNA60283-1484	dendrocytes, spleen, prostate, uterus	hippocampus, substantia nigra, heart
	DNA60619-1482	dendrocytes, substantia nigra, colon tumor	
	DNA60625-1507	cartilage	prostate, brain, heart, colon tumor
		10	. , . ,
	DNA60629-1481	uterus, colon tumor, substantia nigra	hippocampus, dendrocytes, spleen.
		uterus, colon tumor, substantia nigra	hippocampus, dendrocytes, spleen, prostate
55		uterus, colon tumor, substantia nigra dendrocytes, substantia nigra, colon tumor	prostate

DNA Molecule Tissues w/ Significant Expression Tissues w/o Significant Expression DNA64852-1589 prostate, uterus brain, heart, cartilage, colon tumor DNA66308-1537 prostate, heart uterus brain, colon tumor, cartilage DNA68869-1610 spleen, prostate, heart, uterus, colon hippocampus, dendrocytes, prostate tumor, substantia nigra

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EXAMPLE 173: Isolation of cDNA Clones Encoding Human PRO846

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA39949. Based on the DNA39949 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO846.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-CCCTGCAGTGCACCTACAGGGAAG-3' (SEQ ID NO:518)

reverse PCR primer 5'-CTGTCTTCCCCTGCTTGGCTGTGG-3' (SEQ ID NO:519)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA39949 sequence which had the following nucleotide sequence

hybridization probe

5'-GGTGCAGGAAGGGTGGGATCCTCTCTCTCGCTGCTCTGGCCACATC-3' (SEQ ID NO:520)

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In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO846 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO846 [herein designated as DNA44196-1353] (SEQ ID NO:516) and the derived protein sequence for PRO846. The entire nucleotide sequence of UNQ422 (DNA44196-1353) is shown in Figure 329 (SEQ ID

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NO:516). Clone UNQ422 (DNA44196-1353) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 25-27 and ending at the stop codon at nucleotide positions 1021-1023 (Figure 329). The predicted polypeptide precursor is 332 amino acids long (Figure 330). The full-length PRO846 protein shown in Figure 330 has an estimated molecular weight of about 36,143 daltons and a pI of about 5.89. Important regions of the amino acid sequence of PRO846 include the signal peptide, the transmembrane domain, an N-glycosylation site, a sequence typical of fibrinogen beta and gamma chains C-terminal domain, and a sequence typical of Ig like V-type domain as shown in Figure 330. Clone UNQ422 (DNA44196-1353) has been deposited with ATCC and is assigned ATCC deposit no. 209847.

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EXAMPLE 174: Isolation of cDNA Clones Encoding Human PRO363

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA42828. Based on the DNA42828 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO363.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer (42828.fl) 5'-CCAGTGCACAGCAGCAGCAAGCAGCAGCAGC-3' (SEQ ID NO:521)

reverse PCR primer (42828.rl) 5'-ACTAGGCTGTATGCCTGGGTGGGC-3' (SEQ ID NO:522)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA42828 sequence which had the following nucleotide sequence

hybridization probe (42828.p1)

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5'-GTATGTACAAAGCATCGGCATGGTTGCAGGAGCAGTGACAGGC-3' (SEQ ID NO:523)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO363 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO363 [herein designated as UNQ318 (DNA45419-1252)] (SEQ ID NO:500) and the derived protein sequence for PRO363.

The entire nucleotide sequence of UNQ318 (DNA45419-1252) is shown in Figure 313 (SEQ ID NO:500). Clone UNQ318 (DNA45419-1252) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 190-192 and ending at the stop codon at nucleotide positions 1309-1311 (Figure 313). The predicted polypeptide precursor is 373 amino acids long (Figure 314). The full-length PRO363 protein shown in Figure 314 has an estimated molecular weight of about 41,281 daltons and a pI of about 8.33. A transmembrane domain exists at amino acids 221 to 254 of the amino acid sequence shown in Figure 314 (SEQ ID NO:501). The PRO363 polypeptide also possesses at least two myelin P0 protein domains from about amino acids 15 to 56 and from about amino acids 87 to 116. Clone UNQ318 (DNA45419-1252) has been deposited with ATCC on February 5, 1998 and is assigned ATCC deposit no. 209616.

Analysis of the amino acid sequence of the full-length PRO363 polypeptide suggests that it possesses significant sequence similarity to the cell surface protein HCAR, thereby indicating that PRO363 may be a novel HCAR homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO363 amino acid sequence and the following Dayhoff sequences, HS46KDA_1, HSU90716_1, MMCARH_1, MMCARHOM_1, MMU90715_1, A33_HUMAN, P_W14146, P W14188, A42632 and B42632.

EXAMPLE 175: Isolation of cDNA Clones Encoding a Human PRO9828

A consensus DNA sequence was assembled relative to other nucleic sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA139814. Based on the DNA139814 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO9828. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, supra, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

- 5'-AATCTCAGCACCAGCCACTCAGAGCA-3' (SEQ ID NO:524)
- 5'-GTTAAAGAGGGTGCCCTTCCAGCGA-3' (SEQ ID NO:525)
- 15 5'-TATCCCAATGCCTCCCCACTGCTC-3' (SEQ ID NO:526)

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5'-GATGAACTTGGCGAAGGGGCGGCA-3' (SEQ ID NO:527)

RNA for construction of the cDNA libraries was isolated from human fetal liver tissue. The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for a full-length PRO9828 polypeptide (designated herein as DNA142238-2768 [Figure 323, SEQ ID NO:510]) and the derived protein sequence for that PRO9828 polypeptide.

The full length clone identified above contained a single open reading frame with an apparent translational initiation site at nucleotide positions 232-234 and a stop signal at nucleotide positions 985-987. (Figure 323, SEQ ID NO:510). The predicted polypeptide precursor is 251 amino acids long, has a calculated molecular weight of approximately 27,954 daltons and an estimated pI of approximately 9.22. Analysis of the full-length PRO9828 sequence shown in Figure 324 (SEQ ID NO:511) evidences the presence of a variety of important polypeptide domains as shown in Figure 324, wherein the locations given for those important polypeptide domains are approximate as described above. Chromosome mapping evidences that the PRO9828-encoding nucleic acid maps to chromosome 12p13 in humans. Clone DNA142238-2768 has been deposited with ATCC on October 5, 1999 and is assigned ATCC deposit no. 819-PTA.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 324 (SEQ ID NO:511), evidenced sequence

identity between the PRO9828 amino acid sequence and the following Dayhoff sequences: P_Y08581, AB018122_1, FGF3_HUMAN, P_R70824, S54407, P_R80780, P_Y23761, P_W92312, OMFGF6_1 and P_R80871.

EXAMPLE 176: Isolation of cDNA Clones Encoding a Human PRO7170

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DNA108722-2743 was identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., Genbank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals.

Use of the above described signal sequence algorithm allowed identification of an EST cluster sequence from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, designated herein as CLU57836. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., Genbank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA58756.

In light of an observed sequence homology between the DNA58756 sequence and an EST sequence encompassed within clone no. 2251462 from the LIFESEQ® database, Incyte Pharmaceuticals, Palo Alto, CA, clone no. 2251462 was purchased and the cDNA insert was obtained and sequenced. It was found herein that that cDNA insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 325 and is herein designated as DNA108722-2743.

Clone DNA 108722-2743 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 60-62 and ending at the stop codon at nucleotide positions 1506-1508 (Figure 325). The predicted polypeptide precursor is 482 amino acids long (Figure 326). The full-length PRO7170 protein shown in Figure 326 has an estimated molecular weight of about 49,060 daltons and a pI of about 4.74. Analysis of the full-length PRO7170 sequence shown in Figure 326 (SEQ ID NO:513) evidences the presence of a variety of important polypeptide domains as shown in Figure 326, wherein the locations given for those important polypeptide domains are approximate as described above. Clone DNA108722-2743 has been

deposited with ATCC on August 17, 1999 and is assigned ATCC Deposit No. 552-PTA.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 326 (SEQ ID NO:513), evidenced sequence identity between the PRO7170 amino acid sequence and the following Dayhoff sequences: P_Y12291, I47141, D88733_1, DMC56G7_1, P_Y11606, HWP1_CANAL, HSMUC5BEX_1, HSU78550_1, HSU70136_1, and SGS3_DROME.

EXAMPLE 177: Isolation of cDNA Clones Encoding Human PRO361

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA40654. Based on the DNA40654 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO361.

Forward and reverse PCR primers were synthesized as follows:

forward PCR primer	5'-AGGGAGGATTATCCTTGACCTTTGAAGACC-3'	(SEQ ID NO:528)
forward PCR primer	5'-GAAGCAAGTGCCCAGCTC-3'	(SEQ ID NO:529)
forward PCR primer	5'-CGGGTCCCTGCTCTTTGG-3'	(SEQ ID NO:530)
reverse PCR primer	5'-CACCGTAGCTGGGAGCGCACTCAC-3'	(SEQ ID NO:531)
reverse PCR primer	5'-AGTGTAAGTCAAGCTCCC-3'	(SEQ ID NO:532)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40654 sequence which had the following nucleotide sequence

hybridization probe

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5'- GCTTCCTGACACTAAGGCTGTCTGCTAGTCAGAATTGCCTCAAAAAGAG-3' (SEQ ID NO:533)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO361 gene using the probe oligonucleotide. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO361 [herein designated as DNA45410-1250] (SEQ ID NO:514) and the derived protein sequence for PRO361.

The entire nucleotide sequence of DNA45410-1250 is shown in Figure 327 (SEQ ID NO:514). Clone DNA45410-1250 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 226-228 and ending at the stop codon at nucleotide positions 1519-1521 (Figure 327). The predicted polypeptide precursor is 431 amino acids long (Figure 328). The full-length PRO361 protein shown in Figure 328 has an estimated molecular weight of about 46,810 daltons and a pI of about 6.45. In addition, regions of interest including the transmembrane domain (amino acids 380-409) and sequences typical of the arginase family of proteins (amino acids 3-14 and 39-57) are designated in Figure 328. Clone DNA45410-1250 has been deposited with ATCC and is assigned ATCC deposit no. ATCC 209621.

Analysis of the amino acid sequence of the full-length PRO361 polypeptide suggests that portions of it possess significant homology to the mucin and/or chitinase proteins, thereby indicating that PRO361 may be a novel mucin and/or chitinase protein.

EXAMPLE 178: Isolation of cDNA Clones Encoding a Human PRO183, PRO184, PRO185, PRO5723, PRO3301 or PRO9940

DNA molecules encoding the PRO183, PRO184, PRO185, PRO5723, PRO3301 or PRO9940 polypeptides shown in the accompanying figures were obtained through GenBank.

Deposit of Material

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The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC):

		Table 10	
	Material	ATCC Dep. No.	Deposit Date
15	DNA45410-1250	209621	February 5, 1998
	DNA108722-2743	552-PTA	August 17, 1999
	DNA142238-2768	819-PTA	October 5, 1999
	DNA40981-1234	209439	November 7, 1997
	DNA45419-1252	209616	February 5, 1998
20	DNA44196-1353	209847	May 6, 1998
	DNA16422-1209	209929	June 2, 1998
	DNA16435-1208	209930	June 2, 1998
	DNA21624-1391	209917	June 2, 1998
	DNA23334-1392	209918	June 2, 1998
25	DNA26288-1239	209792	April 21, 1998
	DNA26843-1389	203099	August 4, 1998
	DNA26844-1394	209926	June 2, 1998
	DNA30862-1396	209920	June 2, 1998
	DNA35680-1212	209790	April 21, 1998
30	DNA40621-1440	209922	June 2, 1998
	DNA44161-1434	209907	May 27, 1998
	DNA44694-1500	203114	August 11, 1998
	DNA45495-1550	203156	August 25, 1998
	DNA47361-1154	209431	November 7, 1997
35	DNA47394-1572	203109	August 11, 1998
	DNA48320-1433	209904	May 27, 1998
	DNA48334-1435	209924	June 2, 1998
	DNA48606-1479	203040	July 1, 1998
	DNA49141-1431	203003	June 23, 1998
40	DNA49142-1430	203002	June 23, 1998
	DNA49143-1429	203013	June 23, 1998
	DNA49647-1398	209919	June 2, 1998
	DNA49819-1439	209931	June 2, 1998
	DNA49820-1427	209932	June 2, 1998
45	DNA49821-1562	209981	June 16, 1998
	DNA52192-1369	203042	July 1, 1998
	DNA52598-1518	203107	August 11, 1998
	DNA53913-1490	203162	August 25, 1998

		Table 10 (cont')	
	DNA53978-1443	209983	June 16, 1998
	DNA53996-1442	209921	June 2, 1998
	DNA56041-1416	203012	June 23, 1998
	DNA56047-1456	209948	June 9, 1998
5	DNA56050-1455	203011	June 23, 1998
-	DNA56110-1437	203113	August 11, 1998
	DNA56113-1378	203049	July 1, 1998
	DNA56410-1414	209923	June 2, 1998
	DNA56436-1448	209902	May 27, 1998
10	DNA56855-1447	203004	June 23, 1998
10	DNA56859-1445	203019	June 23, 1998
	DNA56860-1510	209952	June 9, 1998
	DNA56865-1491	203022	June 23, 1998
	DNA56866-1342	203022	June 23, 1998
15	DNA56868-1209	203024	June 23, 1998
13	DNA56869-1545	203161	August 25, 1998
	DNA56870-1492	209925	June 2, 1998
	DNA57033-1403	209905	May 27, 1998
	DNA57037-1444	209903	May 27, 1998
20	DNA57129-1413	209977	June 16, 1998
20	DNA57690-1374	209950	June 9, 1998
	DNA57693-1424	203008	June 23, 1998
	DNA57694-1341	203017	June 23, 1998
	DNA57695-1340	203006	June 23, 1998
25	DNA57699-1412	203020	June 23, 1998
20	DNA57702-1476	209951	June 9, 1998
	DNA57704-1452	209953	June 9, 1998
	DNA57708-1411	203021	June 23, 1998
	DNA57710-1451	203048	July 1, 1998
30	DNA57711-1501	203047	July 1, 1998
	DNA57827-1493	203045	July 1, 1998
	DNA57834-1339	209954	June 9, 1998
	DNA57836-1338	203025	June 23, 1998
	DNA57838-1337	203014	June 23, 1998
35	DNA57844-1410	203010	June 23, 1998
	DNA58721-1475	203110	August 11, 1998
	DNA58723-1588	203133	August 18, 1998
	DNA58737-1473	203136	August 18, 1998
	DNA58743-1609	203154	August 25, 1998
40	DNA58846-1409	209957	June 9, 1998
	DNA58848-1472	209955	June 9, 1998
	DNA58849-1494	209958	June 9, 1998
	DNA58850-1495	209956	June 9, 1998
	DNA58853-1423	203016	June 23, 1998
45	DNA58855-1422	203018	June 23, 1998
	DNA59205-1421	203009	June 23, 1998
	DNA59211-1450	209960	June 9, 1998
	DNA59213-1487	209959	June 9, 1998
	DNA59214-1449	203046	July 1, 1998
50	DNA59215-1425	209961	June 9, 1998
	DNA59220-1514	209962	June 9, 1998
	DNA59488-1603	203157	August 25, 1998
	DNA59493-1420	203050	July 1, 1998
	DNA59497-1496	209941	June 4, 1998
55	DNA59588-1571	203106	August 11, 1998

		Table 10 (cont')	
	DNA59603-1419	209944	June 9, 1998
	DNA59605-1418	203005	June 23, 1998
	DNA59606-1471	209945	June 9, 1998
	DNA59607-1497	209957	June 9, 1998
5	DNA59609-1470	209963	June 9, 1998
•	DNA59610-1559	209990	June 16, 1998
	DNA59612-1466	209947	June 9, 1998
	DNA59613-1417	203007	June 23, 1998
	DNA59616-1465	209991	June 16, 1998
10	DNA59619-1464	203041	July 1, 1998
	DNA59620-1463	209989	June 16, 1998
	DNA59625-1498	209992	June 17, 1998
	DNA59767-1489	203108	August 11, 1998
	DNA59776-1600	203128	August 18, 1998
15	DNA59770-1000 DNA59777-1480	203128	August 11, 1998
13	DNA59820-1549	203111	August 18, 1998
	DNA59827-1426	203129	August 4, 1998
	DNA59828-1608	203089	August 25, 1998
	DNA59838-1462	203136	June 16, 1998
20	DNA59839-1461	209976	June 16, 1998
20	DNA59841-1460	203944	July 1, 1998
	DNA59842-1502	209982	June 16, 1998
	DNA59846-1503	209982	June 16, 1998
		203098	August 4, 1998
25	DNA59847-1511 DNA59848-1512	203088	August 4, 1998
23		209986	June 16, 1998
	DNA59849-1504 DNA59853-1505	209985	June 16, 1998
	DNA59854-1459	209983	June 16, 1998
	DNA60283-1484	203974	July 1, 1998
30	DNA60615-1483	203043	June 16, 1998
30	DNA60619-1482	209980	June 16, 1998
	DNA60621-1516	203091	August 4, 1998
	DNA60622-1525	203091	August 4, 1998
	DNA60625-1507	209975	June 16, 1998
35	DNA60627-1508	203092	August 4, 1998
55	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203373	August 11, 1998
	DNA61873-1574	203112	August 18, 1998
	DNA62814-1521	203132	August 4, 1998
40	DNA62872-1509	203100	August 4, 1998
70	DNA62876-1517	203095	August 4, 1998
	DNA62881-1515	203095	August 4, 1998
	DNA64852-1589	203090	August 18, 1998
	DNA64884-1527	203127	August 25, 1998
45	DNA64890-1612	203133	August 18, 1998
73	DNA65412-1523	203131	August 4, 1998
	DNA66308-1537	203054	August 25, 1998
	DNA66309-1538	203133	September 15, 1998
	DNA67004-1614	203253	August 11, 1998
50	DNA68869-1610	203113	August 25, 1998
50	DNA68872-1620	203160	August 25, 1998 August 25, 1998
			August 18, 1998
	DNA71159-1617	203135	August 10, 1990

These deposit were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

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The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

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The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

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1. Isolated nucleic acid having at least 80% sequence identity to a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure

284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) and Figure 330 (SEQ ID NO:517).

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2. The nucleic acid sequence of Claim 1, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of the sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID

NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421), Figure 305 (SEQ ID NO:423), Figure 307 (SEQ ID NO:494), Figure 309 (SEQ ID NO:496), Figure 311 (SEQ ID NO:498), Figure 313 (SEQ ID NO:500), Figure 315 (SEQ ID NO:502), Figure 317 (SEQ ID NO:504), Figure 319 (SEQ ID NO:506), Figure 321 (SEQ ID NO:508), Figure 323 (SEQ ID NO:510), Figure 325 (SEQ ID NO:512), Figure 327 (SEQ ID NO:514) and Figure 329 (SEQ ID NO:516).

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3. The nucleic acid of Claim 1, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of the full-length coding sequence of the sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure

181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEO ID NO:271), Figure 191 (SEO ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEO ID NO:292), Figure 211 (SEO ID NO:294), Figure 213 (SEO ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421), Figure 305 (SEQ ID NO:423), Figure 307 (SEQ ID NO:494), Figure 309 (SEQ ID NO:496), Figure 311 (SEQ ID NO:498), Figure 313 (SEQ ID NO:500), Figure 315 (SEQ ID NO:502), Figure 317 (SEQ ID NO:504), Figure 319 (SEQ ID NO:506), Figure 321 (SEQ ID NO:508), Figure 323 (SEQ ID NO:510), Figure 325 (SEQ ID NO:512), Figure 327 (SEQ ID NO:514) and Figure 329 (SEQ ID NO:516).

- 4. Isolated nucleic acid which comprises the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 10.
- A vector comprising the nucleic acid of Claim 1.

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- 6. The vector of Claim 5 operably linked to control sequences recognized by a host cell transformed with the vector.
- A host cell comprising the vector of Claim 5.
 - 8. The host cell of Claim 7 wherein said cell is a CHO cell.
 - 9. The host cell of Claim 7 wherein said cell is an E. coli.
 - 10. The host cell of Claim 7 wherein said cell is a yeast cell.

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11. A process for producing a PRO polypeptides comprising culturing the host cell of Claim 7 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

12. Isolated PRO polypeptide having at least 80% sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEO ID NO:211), Figure 141 (SEO ID NO:213), Figure 144 (SEO ID NO:216), Figure 147 (SEO ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID

NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) and Figure 330 (SEQ ID NO:517).

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- 13. Isolated PRO polypeptide having at least 80% sequence identity to the amino acid sequence encoded by a nucleic acid molecule deposited under any ATCC accession number shown in Table 10.
- 14. A chimeric molecule comprising a polypeptide according to Claim 12 fused to a heterologous
 amino acid sequence.
 - 15. The chimeric molecule of Claim 14 wherein said heterologous amino acid sequence is an epitope tag sequence.
- 20 16. The chimeric molecule of Claim 14 wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.
 - 17. An antibody which specifically binds to a PRO polypeptide according to Claim 12.
 - 18. The antibody of Claim 17 wherein said antibody is a monoclonal antibody.
 - 19. The antibody of Claim 17 wherein said antibody is a humanized antibody.
 - 20. The antibody of Claim 17 wherein said antibody is an antibody fragment.

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An isolated nucleic acid molecule which has at least 80% sequence identity to a nucleic acid which comprises a nucleotide sequence selected from the group consisting of that shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50

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(SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID . NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421), Figure 305 (SEQ ID NO:423), Figure 307 (SEQ ID NO:494), Figure 309 (SEQ ID NO:496), Figure 311 (SEQ ID NO:498), Figure 313 (SEQ ID NO:500), Figure 315 (SEQ ID NO:502), Figure 317 (SEQ ID NO:504), Figure 319 (SEQ ID NO:506), Figure 321 (SEQ ID NO:508), Figure 323 (SEQ ID NO:510), Figure 325 (SEQ ID NO:512), Figure 327 (SEQ ID NO:514) and Figure 329 (SEQ ID NO:516).

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22. An isolated nucleic acid molecule which has at least 80% sequence identity to the full-length coding sequence of a nucleotide sequence selected from the group consisting of that shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEO ID NO:51), Figure 33 (SEO ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEO ID NO:114), Figure 67 (SEO ID NO:116), Figure 69 (SEO ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure

293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421), Figure 305 (SEQ ID NO:423), Figure 307 (SEQ ID NO:494), Figure 309 (SEQ ID NO:496), Figure 311 (SEQ ID NO:498), Figure 313 (SEQ ID NO:500), Figure 315 (SEQ ID NO:502), Figure 317 (SEQ ID NO:504), Figure 319 (SEQ ID NO:506), Figure 321 (SEQ ID NO:508), Figure 323 (SEQ ID NO:510), Figure 325 (SEQ ID NO:512), Figure 327 (SEQ ID NO:514) and Figure 329 (SEQ ID NO:516).

- 23. An isolated extracellular domain of of PRO polypeptide.
- 24. An isolated PRO polypeptide lacking its associated signal peptide.

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- 25. An isolated polypeptide having at least about 80% amino acid sequence identity to an extracellular domain of of PRO polypeptide.
- 26. An isolated polypeptide having at least about 80% amino acid sequence identity to a PRO polypeptide lacking its associated signal peptide.
 - 27. Isolated nucleic acid having at least 80% nucleic acid sequence identity to:
 - a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure

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169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) or Figure 330 (SEQ ID NO:517), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID

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NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) or Figure 330 (SEQ ID NO:517), with its associated signal peptide; or

(c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:131), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure

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90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) or Figure 330 (SEQ ID NO:517), lacking its associated signal peptide.

- 28. An isolated polypeptide having at least 80% amino acid sequence identity to:
- (a) the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36),

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Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEO ID NO:62), Figure 38 (SEO ID NO:67), Figure 41 (SEO ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID

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NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) or Figure 330 (SEQ ID NO:517), lacking its associated signal peptide;

(b) an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID

NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) or Figure 330 (SEQ ID NO:517), with its associated signal peptide; or

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an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ (c) ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEO ID NO:84), Figure 49 (SEO ID NO:95), Figure 51 (SEO ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure

254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422), Figure 306 (SEQ ID NO:424), Figure 308 (SEQ ID NO:495), Figure 310 (SEQ ID NO:497), Figure 312 (SEQ ID NO:499), Figure 314 (SEQ ID NO:501), Figure 316 (SEQ ID NO:503), Figure 318 (SEQ ID NO:505), Figure 320 (SEQ ID NO:507), Figure 322 (SEQ ID NO:509), Figure 324 (SEQ ID NO:511), Figure 326 (SEQ ID NO:513), Figure 328 (SEQ ID NO:515) or Figure 330 (SEQ ID NO:517), lacking its associated signal peptide.

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- 29. A method of detecting a PRO943 polypeptide in a sample suspected of containing a PRO943 polypeptide, said method comprising contacting said sample with a PRO183, PRO184 or PRO185 polypeptide and determining the formation of a PRO943/PRO183, PRO184 or PRO185 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO943 polypeptide in said sample.
- 30. The method according to Claim 29, wherein said sample comprises cells suspected of expressing said PRO943 polypeptide.
 - 31. The method according to Claim 29, wherein said PRO183, PRO184 or PRO185 polypeptide is labeled with a detectable label.
 - 32. The method according to Claim 29, wherein said PRO183, PRO184 or PRO185 polypeptide is attached to a solid support.
 - 33. A method of detecting a PRO183, PRO184 or PRO185 polypeptide in a sample suspected of containing a PRO183, PRO184 or PRO185 polypeptide, said method comprising contacting said sample with a PRO943 polypeptide and determining the formation of a PRO943/PRO183, PRO184 or PRO185 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO183, PRO184 or PRO185 polypeptide in said sample.
- 34. The method according to Claim 33, wherein said sample comprises cells suspected of expressing said PRO183, PRO184 or PRO185 polypeptide.

35. The method according to Claim 33, wherein said PRO943 polypeptide is labeled with a detectable label.

36. The method according to Claim 33, wherein said PRO943 polypeptide is attached to a solid support.

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37. A method of detecting a PRO331 polypeptide in a sample suspected of containing a PRO331 polypeptide, said method comprising contacting said sample with a PRO1133 polypeptide and determining the formation of a PRO331/PRO1133 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO331 polypeptide in said sample.

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- 38. The method according to Claim 37, wherein said sample comprises cells suspected of expressing said PRO331 polypeptide.
- 39. The method according to Claim 37, wherein said PRO1133 polypeptide is labeled with adetectable label.
 - 40. The method according to Claim 37, wherein said PRO1133 polypeptide is attached to a solid support.

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41. A method of detecting a PRO1133 polypeptide in a sample suspected of containing a PRO1133 polypeptide, said method comprising contacting said sample with a PRO331 polypeptide and determining the formation of a PRO331/PRO1133 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO1133 polypeptide in said sample.

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- 42. The method according to Claim 41, wherein said sample comprises cells suspected of expressing said PRO1133 polypeptide.
- 43. The method according to Claim 41, wherein said PRO331 polypeptide is labeled with a detectable label.

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44. The method according to Claim 41, wherein said PRO331 polypeptide is attached to a solid support.

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45. A method of detecting a PRO363 or PRO5723 polypeptide in a sample suspected of containing a PRO363 or PRO5723 polypeptide, said method comprising contacting said sample with a PRO1387 polypeptide and determining the formation of a PRO363 or PRO5723/PRO1387 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO363

or PRO5723 polypeptide in said sample.

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46. The method according to Claim 45, wherein said sample comprises cells suspected of expressing said PRO363 or PRO5723 polypeptide.

- 5 47. The method according to Claim 45, wherein said PRO1387 polypeptide is labeled with a detectable label.
 - 48. The method according to Claim 45, wherein said PRO1387 polypeptide is attached to a solid support.
 - 49. A method of detecting a PRO1387 polypeptide in a sample suspected of containing a PRO1387 polypeptide, said method comprising contacting said sample with a PRO363 or PRO5723 polypeptide and determining the formation of a PRO363 or PRO5723/PRO1387 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO1387 polypeptide in said sample.
 - 50. The method according to Claim 49, wherein said sample comprises cells suspected of expressing said PRO1387 polypeptide.
- 51. The method according to Claim 49, wherein said PRO363 or PRO5723 polypeptide is labeled with a detectable label.
 - 52. The method according to Claim 49, wherein said PRO363 or PRO5723 polypeptide is attached to a solid support.
- 25 53. A method of detecting a PRO1114 polypeptide in a sample suspected of containing a PRO1114 polypeptide, said method comprising contacting said sample with a PRO3301 or PRO9940 polypeptide and determining the formation of a PRO1114/PRO3301 or PRO9940 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO1114 polypeptide in said sample.
 - 54. The method according to Claim 53, wherein said sample comprises cells suspected of expressing said PRO1114 polypeptide.
- 55. The method according to Claim 53, wherein said PRO3301 or PRO9940 polypeptide is labeled with a detectable label.

56. The method according to Claim 53, wherein said PRO3301 or PRO9940 polypeptide is attached to a solid support.

57. A method of detecting a PRO3301 or PRO9940 polypeptide in a sample suspected of containing a PRO3301 or PRO9940 polypeptide, said method comprising contacting said sample with a PRO1114 polypeptide and determining the formation of a PRO3301 or PRO9940/PRO1114 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO3301 or PRO9940 polypeptide in said sample.

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- 58. The method according to Claim 57, wherein said sample comprises cells suspected of expressing said PRO3301 or PRO9940 polypeptide.
 - 59. The method according to Claim 57, wherein said PRO1114 polypeptide is labeled with a detectable label.
- The method according to Claim 57, wherein said PRO1114 polypeptide is attached to a solid support.
 - 61. A method of detecting a PRO1181 polypeptide in a sample suspected of containing a PRO1181 polypeptide, said method comprising contacting said sample with a PRO7170, PRO361 or PRO846 polypeptide and determining the formation of a PRO1181/PRO7170, PRO361 or PRO846 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO1181 polypeptide in said sample.
- 62. The method according to Claim 61, wherein said sample comprises cells suspected of expressing said PRO1181 polypeptide.
 - 63. The method according to Claim 61, wherein said PRO7170, PRO361 or PRO846 polypeptide is labeled with a detectable label.
- The method according to Claim 61, wherein said PRO7170, PRO361 or PRO846 polypeptide is attached to a solid support.
 - 65. A method of detecting a PRO7170, PRO361 or PRO846 polypeptide in a sample suspected of containing a PRO7170, PRO361 or PRO846 polypeptide, said method comprising contacting said sample with a PRO1181 polypeptide and determining the formation of a PRO1181/PRO7170, PRO361 or PRO846 polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of a PRO7170, PRO361 or PRO846 polypeptide in said sample.

66. The method according to Claim 65, wherein said sample comprises cells suspected of expressing said PRO7170, PRO361 or PRO846 polypeptide.

67. The method according to Claim 65, wherein said PRO1181 polypeptide is labeled with a detectable label.

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68. The method according to Claim 65, wherein said PRO1181 polypeptide is attached to a solid support.

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69. A method of linking a bioactive molecule to a cell expressing a PRO943 polypeptide, said method comprising contacting said cell with a PRO183, PRO184 or PRO185 polypeptide that is bound to said bioactive molecule and allowing said PRO943 and PRO183, PRO184 or PRO185 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.

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70. The method according to Claim 69, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

71. The method according to Claim 69, wherein said bioactive molecule causes the death of said cell.

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72. A method of linking a bioactive molecule to a cell expressing a PRO183, PRO184 or PRO185 polypeptide, said method comprising contacting said cell with a PRO943 polypeptide that is bound to said bioactive molecule and allowing said PRO943 and PRO183, PRO184 or PRO185 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.

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73. The method according to Claim 72, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

74. The method according to Claim 73, wherein said bioactive molecule causes the death of said cell.

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75. A method of linking a bioactive molecule to a cell expressing a PRO331 polypeptide, said method comprising contacting said cell with a PRO1133 polypeptide that is bound to said bioactive molecule and allowing said PRO331 and PRO1133 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.

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76. The method according to Claim 75, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

77. The method according to Claim 75, wherein said bioactive molecule causes the death of said cell.

- 78. A method of linking a bioactive molecule to a cell expressing a PRO1133 polypeptide, said method comprising contacting said cell with a PRO331 polypeptide that is bound to said bioactive molecule and allowing said PRO331 and PRO1133 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.
- 79. The method according to Claim 78, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

80. The method according to Claim 78, wherein said bioactive molecule causes the death of said cell.

- 81. A method of linking a bioactive molecule to a cell expressing a PRO1387 polypeptide, said method comprising contacting said cell with a PRO363 or PRO5723 polypeptide that is bound to said bioactive molecule and allowing said PRO1387 and PRO363 or PRO5723 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.
- 82. The method according to Claim 81, wherein said bioactive molecule is a toxin, a radiolabel 20 or an antibody.
 - 83. The method according to Claim 81, wherein said bioactive molecule causes the death of said cell.
- A method of linking a bioactive molecule to a cell expressing a PRO363 or PRO5723 polypeptide, said method comprising contacting said cell with a PRO1387 polypeptide that is bound to said bioactive molecule and allowing said PRO1387 and PRO363 or PRO5723 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.
- The method according to Claim 84, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.
 - 86. The method according to Claim 84, wherein said bioactive molecule causes the death of said cell.

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87. A method of linking a bioactive molecule to a cell expressing a PRO1114 polypeptide, said method comprising contacting said cell with a PRO3301 or PRO9940 polypeptide that is bound to said bioactive molecule and allowing said PRO1114 and PRO3301 or PRO9940 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.

- 5 88. The method according to Claim 87, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.
 - 89. The method according to Claim 87, wherein said bioactive molecule causes the death of said cell.

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90. A method of linking a bioactive molecule to a cell expressing a PRO3301 or PRO9940 polypeptide, said method comprising contacting said cell with a PRO1114 polypeptide that is bound to said bioactive molecule and allowing said PRO1114 and PRO3301 or PRO9940 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.

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- 91. The method according to Claim 90, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.
- 92. The method according to Claim 90, wherein said bioactive molecule causes the death of said20 cell.
 - 93. A method of linking a bioactive molecule to a cell expressing a PRO1181 polypeptide, said method comprising contacting said cell with a PRO7170, PRO361 or PRO846 polypeptide that is bound to said bioactive molecule and allowing said PRO1181 and PRO7170, PRO361 or PRO846 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.
 - 94. The method according to Claim 93, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.
- The method according to Claim 93, wherein said bioactive molecule causes the death of said cell.
- 96. A method of linking a bioactive molecule to a cell expressing a PRO7170, PRO361 or PRO846 polypeptide, said method comprising contacting said cell with a PRO1181 polypeptide that is bound to said bioactive molecule and allowing said PRO1181 and PRO7170, PRO361 or PRO846 polypeptides to bind to one another, thereby linking said bioactive molecules to said cell.

97. The method according to Claim 96, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

98. The method according to Claim 96, wherein said bioactive molecule causes the death of said cell.

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99. A method of modulating at least one biological activity of a cell expressing a PRO943 polypeptide, said method comprising contacting said cell with a PRO183, PRO184 or PRO185 polypeptide or an anti-PRO943 antibody, whereby said PRO183, PRO184 or PRO185 polypeptide or said anti-PRO943 antibody binds to said PRO943 polypeptide, thereby modulating at least one biological activity of said cell.

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- 100. The method according to Claim 99, wherein said cell is killed.
- 101. A method of modulating at least one biological activity of a cell expressing a PRO183, PRO184 or PRO185 polypeptide, said method comprising contacting said cell with a PRO943 polypeptide or an anti-PRO183, anti-PRO184 or anti-PRO185 antibody, whereby said PRO943 polypeptide or said anti-PRO183, anti-PRO184 or anti-PRO185 antibody binds to said PRO183, PRO184 or PRO185 polypeptide, thereby modulating at least one biological activity of said cell.
 - 102. The method according to Claim 101, wherein said cell is killed.

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103. A method of modulating at least one biological activity of a cell expressing a PRO331 polypeptide, said method comprising contacting said cell with a PRO1133 polypeptide or an anti-PRO331 antibody, whereby said PRO1133 polypeptide or said anti-PRO331 antibody binds to said PRO331 polypeptide, thereby modulating at least one biological activity of said cell.

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- 104. The method according to Claim 103, wherein said cell is killed.
- 105. A method of modulating at least one biological activity of a cell expressing a PRO1133 polypeptide, said method comprising contacting said cell with a PRO331 polypeptide or an anti-PRO1133 antibody, whereby said PRO331 polypeptide or said anti-PRO1133 antibody binds to said PRO1133 polypeptide, thereby modulating at least one biological activity of said cell.
 - 106. The method according to Claim 105, wherein said cell is killed.

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107. A method of modulating at least one biological activity of a cell expressing a PRO1387 polypeptide, said method comprising contacting said cell with a PRO363 or PRO5723 polypeptide or an anti-PRO1387 antibody, whereby said PRO363 or PRO5723 polypeptide or said anti-PRO1387 antibody binds to said PRO1387 polypeptide, thereby modulating at least one biological activity of said cell.

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- 108. The method according to Claim 107, wherein said cell is killed.
- 109. A method of modulating at least one biological activity of a cell expressing a PRO363 or PRO5723 polypeptide, said method comprising contacting said cell with a PRO1387 polypeptide or an anti-PRO363 or anti-PRO5723 antibody, whereby said PRO1387 polypeptide or said anti-PRO363 or anti-PRO5723 antibody binds to said PRO363 or PRO5723 polypeptide, thereby modulating at least one biological activity of said cell.
 - 110. The method according to Claim 109, wherein said cell is killed.

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111. A method of modulating at least one biological activity of a cell expressing a PRO1114 polypeptide, said method comprising contacting said cell with a PRO3301 or PRO9940 polypeptide or an anti-PRO1114 antibody, whereby said PRO3301 or PRO9940 polypeptide or said anti-PRO1114 antibody binds to said PRO1114 polypeptide, thereby modulating at least one biological activity of said cell.

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- 112. The method according to Claim 111, wherein said cell is killed.
- PRO9940 polypeptide, said method comprising contacting said cell with a PRO1114 polypeptide or an anti-PRO3301 or anti-PRO9940 antibody, whereby said PRO1114 polypeptide or said anti-PRO3301 or anti-PRO9940 antibody binds to said PRO3301 or PRO9940 polypeptide, thereby modulating at least one biological activity of said cell.
 - 114. The method according to Claim 113, wherein said cell is killed.

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115. A method of modulating at least one biological activity of a cell expressing a PRO1181 polypeptide, said method comprising contacting said cell with a PRO7170, PRO361 or PRO846 polypeptide or an anti-PRO1181 antibody, whereby said PRO7170, PRO361 or PRO846 polypeptide or said anti-PRO1181 antibody binds to said PRO1181 polypeptide, thereby modulating at least one biological activity of said cell.

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116. The method according to Claim 115, wherein said cell is killed.

117. A method of modulating at least one biological activity of a cell expressing a PRO7170, PRO361 or PRO846 polypeptide, said method comprising contacting said cell with a PRO1181 polypeptide or an anti-PRO7170, anti-PRO361 or anti-PRO846 antibody, whereby said PRO1181 polypeptide or said anti-PRO7170, anti-PRO361 or anti-PRO846 antibody binds to said PRO7170, PRO361 or PRO846 polypeptide, thereby modulating at least one biological activity of said cell.

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118. The method according to Claim 117, wherein said cell is killed.

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FIGURE 1

CGGACGCGTGGGTGCGAGGCGAAGGTGACCGGGGACCGAGCATTTCAGATCTGCTCGGTAGA CCTGGTGCACCACCATGTTGGCTGCAAGGCTGGTGTCTCCCGGACACTACCTTCTAGG GTTTTCCACCCAGCTTTCACCAAGGCCTCCCCTGTTGTGAAGAATTCCATCACGAAGAATCA ATGGCTGTTAACACCTAGCAGGGAATATGCCACCAAAACAAGAATTGGGATCCGGCGTGGGA GAACTGGCCAAGAACTCAAAGAGGCAGCATTGGAACCATCGATGGAAAAAATATTTAAAATT GATCAGATGGGAAGATGGTTTGTTGCTGGAGGGGCTGCTGTTGGTCTTTGGAGCATTGTGCTA CTATGGCTTGGGACTGTCTAATGAGATTGGAGCTATTGAAAAGGCTGTAATTTGGCCTCAGT ATGTCAAGGATAGAATTCATTCCACCTATATGTACTTAGCAGGGAGTATTGGTTTAACAGCT TTGTCTGCCATAGCAATCAGCAGAACGCCTGTTCTCATGAACTTCATGATGAGAGGCTCTTG GGTGACAATTGGTGTGACCTTTGCAGCCATGGTTGGAGCTGGAATGCTGGTACGATCAATAC CATATGACCAGAGCCCAGGCCCAAAGCATCTTGCTTGGTTGCTACATTCTGGTGTGATGGGT GCAGTGGTGGCTCCTCTGACAATATTAGGGGGTCCTCTTCTCATCAGAGCTGCATGGTACAC AGCTGGCATTGTGGGAGGCCTCTCCACTGTGGCCATGTGTGCGCCCAGTGAAAAGTTTCTGA ACATGGGTGCACCCCTGGGAGTGGGCCTGGGTCTCGTCTTTGTGTCCTCATTGGGATCTATG TTTCTTCCACCTACCACCGTGGCTGGTGCCACTCTTTACTCAGTGGCAATGTACGGTGGATT AGTTCTTTTCAGCATGTTCCTTCTGTATGATACCCAGAAAGTAATCAAGCGTGCAGAAGTAT CACCAATGTATGGAGTTCAAAAATATGATCCCATTAACTCGATGCTGAGTATCTACATGGAT **A**AGTGACTCAGCTTCTGGCTTCTCTGCTACATCAAATATCTTGTTTAATGGGGCAGATATGC ATTAAATAGTTTGTACAAGCAGCTTTCGTTGAAGTTTAGAAGATAAGAAACATGTCATCATA TTTAAATGTTCCGGTAATGTGATGCCTCAGGTCTGCCTTTTTTTCTGGAGAATAAATGCAGT AATCCTCTCCCAAATAAGCACACACTTTTCAATTCTCATGTTTGAGTGATTTTAAAATGTT TTGGTGAATGTGAAAACTAAAGTTTGTGTCATGAGAATGTAAGTCTTTTTTCTACTTTAAAA TTTAGTAGGTTCACTGAGTAACTAAAATTTAGCAAACCTGTGTTTGCATATTTTTTTGGAGT GCAGAATATTGTAATTAATGTCATAAGTGATTTGGAGCTTTGGTAAAGGGACCAGAGAGAAG GAGTCACCTGCAGTCTTTTGTTTTTTAAATACTTAGAACTTAGCACTTGTGTTATTGATTA GCTGAACTTAACAAAACTGTTCATCCTGAAACAGGCACAGGTGATGCATTCTCCTGCTGTTG CTTCTCAGTGCTCTTTTCCAATATAGATGTGGTCATGTTTGACTTGTACAGAATGTTAATC ATACAGAGAATCCTTGATGGAATTATATATGTGTGTTTTTACTTTTGAATGTTACAAAAGGAA ATAACTTTAAAACTATTCTCAAGAGAAAATATTCAAAGCATGAAATATGTTGCTTTTTCCAG **AATACAAACAGTATACTCATG**

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FIGURE 2

MLAARLVCLRTLPSRVFHPAFTKASPVVKNSITKNQWLLTPSREYATKTRIGIRRGRTGQEL KEAALEPSMEKIFKIDQMGRWFVAGGAAVGLGALCYYGLGLSNEIGAIEKAVIWPQYVKDRI HSTYMYLAGSIGLTALSAIAISRTPVLMNFMMRGSWVTIGVTFAAMVGAGMLVRSIPYDQSP GPKHLAWLLHSGVMGAVVAPLTILGGPLLIRAAWYTAGIVGGLSTVAMCAPSEKFLNMGAPL GVGLGLVFVSSLGSMFLPPTTVAGATLYSVAMYGGLVLFSMFLLYDTQKVIKRAEVSPMYGV QKYDPINSMLSIYMDTLNIFMRVATMLATGGNRKK

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FIGURE 3

GAAGGCTGCCTCGCTGGTCCGAATTCGGTGGCGCCACGTCCGCCCGTCTCCGCCTTCTGCAT CGCĞCTTCGGCGCTTCCACCTAGACACTCGCGGAĞCCGGCCGCGTCGTGAGGG GGTCGGCACGGGGAGTCGGGCGGTCTTGTGCATCTTGGCTACCTGTGGGTCGAAG<u>ATG</u>TCGG ACATCGGAGACTGGTTCAGGAGCATCCCGGCGATCACGCGCTATTGGTTCGCCGCCACCGTC GCCGTGCCCTTGGTCGGCAAACTCGGCCTCATCAGCCCGGCCTACCTCTTCCTCTGGCCCGA TGTCAGTACTTTATGTCTGGGCCCAGCTGAACAGAGACATGATTGTATCATTTTGGTTTGGA TGCTGATCAGAATGGCGGAGGCGGGAGACACAACTGGGGCCAGGGCTTTCGACTTGGAGACC AG<u>TGAAGGGGGGCCTCGGGCAGCCGCTCCTCTCAAGCCACATTTCCTCCCAGTGCTGGGTG</u> CACTTAACAACTGCGTTCTGGCTAACACTGTTGGACCTGACCCACACTGAATGTAGTCTTTC AGTACGAGACAAAGTTTCTTAAATCCCGAAGAAAAATATAAGTGTTCCACAAGTTTCACGAT TCTCATTCAAGTCCTTACTGCTGTGAAGAACAAATACCAACTGTGCAAATTGCAAAACTGAC TACATTTTTTGGTGTCTTCTCTCTCCCCTTTCCGTCTGAATAATGGGTTTTAGCGGGTCCT AATCTGCTGGCATTGAGCTGGGGCTGGGTCACCAAACCCTTCCCAAAAGGACCTTATCTCTT TCTTGCACACATGCCTCTCCCACTTTTCCCAACCCCCACATTTGCAACTAGAAAAAGTTG CAGATTGGTTATTAATGAGATACTAGGTTGGTGTTTTGTTTCCTGAGCTAAGTGA TCAAGACTGTAGTGGAGTTGCAGCTAACATGGGTTAGGTTTAAACCATGGGGGATGCACCCC TTTGCGTTTCATATGTAGCCCTACTGGCTTTGTGTAGCTGGAGTAGTTGGGTTGCTTTGTGT TAGGAGGATCCAGATCATGTTGGCTACAGGGAGATGCTCTCTTTTGAGAGGTCCTGGGCATTG GAGGAAGGCGCAGCTCCTCTCTGCACGTAGATCATTTTTTAAAGCTAATGTAAGCACATCTA AGGGAATAACATGATTTAAGGTTGAAATGGCTTTAGAATCATTTTGGGTTTGAGGGTGTGTTA TTTTGAGTCATGAATGTACAAGCTCTGTGAATCAGACCAGCTTAAATACCCACACCTTTTTT TTCAGGAAACATTGTGCTCTAACAGTATGACTATTCTTTCCCCCACTCTTAAACAGTGTGAT ATGAAGTTATTCCTCTTAAACATGGTTAGGAAGCTGATGACGTTATTGATTTTGTCTGGATT TTTTTGTAAACTAATCCTTTTTATTGGTAAAAATTGTAAATTAAAATGTGCAACTTG

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FIGURE 4

MSDIGDWFRSIPAITRYWFAATVAVPLVGKLGLISPAYLFLWPEAFLYRFQIWRPITATFYF PVGPGTGFLYLVNLYFLYQYSTRLETGAFDGRPADYLFMLLFNWICIVITGLAMDMQLLMIP LIMSVLYVWAQLNRDMIVSFWFGTRFKACYLPWVILGFNYIIGGSVINELIGNLVGHLYFFL MFRYPMDLGGRNFLSTPQFLYRWLPSRRGGVSGFGVPPASMRRAADQNGGGGRHNWGQGFRL GDQ

Transmembrane domain:

amino acids 98-116, 152-172

N-myristoylation site.

amino acids 89-95, 168-174, 176-182, 215-221, 221-227, 237-243

Glycosaminoglycan attachment site.

amino acids 218-222

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FIGURE 5

GGGGCCGCGGTCTAGGGCGGCTACGTGTTTCCCATAGCGACCATTTTGCATTAACTGGTTG GTAGCTTCTATCCTGGGGGCTGAGCGACTGCGGGCCAGCTCTTCCCCTACTCCCTCTCGGCT CCTTGTGGCCCAAAGGCCTAACCGGGGTCCGGCGGTCTGGCCTAGGGATCTTCCCCGTTGCC CCTTTGGGGCGGGATGGCTGCGGAAGAAGAAGACGAGGTGGAGTGGGTAGTGGAGAGCATCG CGGGGTTCCTGCGAGGCCCAGACTGGTCCATCCCCATCTTGGACTTTGTGGAACAGAAATGT GAAGTTAACTGCAAAGGAGGCCATGTGATAACTCCAGGAAGCCCAGAGCCGGTGATTTTGGT GGCCTGTGTTCCCCTTGTTTTTGATGATGAAGAAGAAAGCAAATTGACCTATACAGAGATTC ATCAGGAATACAAAGAACTAGTTGAAAAGCTGTTAGAAGGTTACCTCAAAGAAATTGGAATT AATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGCAAAGACCCATACATCACAGGC CATTTTGCAACCTGTGTTGGCAGCAGAAGATTTTACTATCTTTAAAGCAATGATGGTCCAGA AAAACATTGAAATGCAGCTGCAAGCCATTCGAATAATTCAAGAGAGAAATGGTGTATTACCT GACTGCTTAACCGATGGCTCTGATGTGGTCAGTGACCTTGAACACGAAGAGATGAAAATCCT GAGGGAAGTTCTTAGAAAATCAAAAGAGGAATATGACCAGGAAGAAGAAAGGAAGAGGAAAAA AACAGTTATCAGAGGCTAAAACAGAAGAGCCCACAGTGCATTCCAGTGAAGCTGCAATAATG CACAAAAAGGCCTGAAGATTCCTGGCTTAGAGCATGCGAGCATTGAAGGACCAATAGCAAAC TAAGTTGATGTCCATGAGAAAGGATATGAGGACTAAACAGATACAAAATATGGAGCAGAAAG GAAAACCCACTGGGGAGGTAGAGGAAATGACAGAGAAACCAGAAATGACAGCAGAGGAGAAG CAAACATTACTAAAGAGGAGATTGCTTGCAGAGAAACTCAAAGAAGAAGTTATTAATAAG**TA CTTACACTG**

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FIGURE 6

MAAEEEDEVEWVVESIAGFLRGPDWSIPILDFVEQKCEVNCKGGHVITPGSPEPVILVACVP LVFDDEEESKLTYTEIHQEYKELVEKLLEGYLKEIGINEDQFQEACTSPLAKTHTSQAILQP VLAAEDFTIFKAMMVQKNIEMQLQAIRIIQERNGVLPDCLTDGSDVVSDLEHEEMKILREVL RKSKEEYDQEEERKRKKQLSEAKTEEPTVHSSEAAIMNNSQGDGEHFAHPPSEVKMHFANQS IEPLGRKVERSETSSLPQKGLKIPGLEHASIEGPIANLSVLGTEELRQREHYLKQKRDKLMS MRKDMRTKQIQNMEQKGKPTGEVEEMTEKPEMTAEEKQTLLKRRLLAEKLKEEVINK

N-glycosylation sites.

amino acids 224-228, 246-250, 285-289

N-myristoylation site.

amino acids 273-279

Amidation site.

amino acids 252-256

Cytosolic fatty-acid binding proteins.

amino acids 78-108

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FIGURE 7

GGGCACAGCACATGTGAAGTTTTTGATGATGAAGAAGAAAGCAAATTGACCTATACAGAGAT
TCATCAGGAATACAAAGAACTAGTTGAAAAAGCTGTTAGAAGGTTACCTCAAAGAAATTGGAA
TTAATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGCAAAGACCCATACATCACAG
GCCATTTTTGCAACCTGTGTTGGCAGCAGAAGATTTTACTATCTTTAAAGCAATGATGGTCC
AGAAAAACATTGAAATGCAGCTGCAAGCCATTCGAATAATTCAAGAGAGAAATGGTGTATTA
CCTGACTGCTTAACCGATGGCTCTGATGTGGTCAGTGACCTTGAACACGAAGAGATGAAAAT
CCTGAGGGAAGTTCTTAGAAAATCAAAAGAGGAATATTGACCAGGAA

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FIGURE 8

TAGCTTCTCCACGTATGGACCCTAAAGGCTACTGCTGCTACTACGGGGCTAGACAGTTACTG AGTGGA**ATG**GAAAAACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCAACAATGTATAC ATTCCTGCTAGGTGCCATATTCATTGCTTTAAGCTCAAGTCGCATCTTACTAGTGAAGTATT CTGCCAATGAAGAAACAAGTATGATTATCTTCCAACTACTGTGAATGTGTGCTCAGAACTG AAATTTGAAATATGCTTCCTGGAAGGAATTCTCTGATTTCATGAAGTGGTCCATTCCTGCCT TTCTTTATTTCCTGGATAACTTGATTGTCTTCTATGTCCTGTCCTATCTTCAACCAGCCATG GCTGTTATCTTCAAATTTTAGCATTATAACAACAGCTCTTCTATTCAGGATAGTGCTGAA GAGGCGTCTAAACTGGATCCAGTGGGCTTCCCTCCTGACTTTATTTTTTGTCTATTGTGGCCT TGACTGCCGGGACTAAAACTTTACAGCACAACTTGGCAGGACGTGGATTTCATCACGATGCC TACAGCAAAGGAATGGACTTTTCCTGAAGCTAAATGGAACACCACAGCCAGAGTTTTCAGTC ACATCCGTCTTGGCATGGGCCATGTTCTTATTATAGTCCAGTGTTTTATTTCTTCAATGGCT AATATCTATAATGAAAAGATACTGAAGGAGGGGAACCAGCTCACTGAAAGCATCTTCATACA GAACAGCAAACTCTATTTCTTTGGCATTCTGTTTAATGGGCTGACTCTGGGCCTTCAGAGGA CTTATTTTTGTAACTGCATTCCAGGGCCTTTCAGTGGCTTTCATTCTGAAGTTCCTGGATAA TCTTTGACTTCAGGCCCTCCCTGGAATTTTTCTTGGAAGCCCCATCAGTCCTTCTCTCTATA TTTATTTATAATGCCAGCAAGCCTCAAGTTCCGGAATACGCACCTAGGCAAGAAAGGATCCG AGATCTAAGTGGCAATCTTTGGGAGCGTTCCAGTGGGGATGGAGAAGAACTAGAAAGACTTA CCAAACCCAAGAGTGATGAGTCAGATGAAGATACTTTC<u>TAA</u>CTGGTACCCACATAGTTTGCA GCTCTCTTGAACCTTATTTTCACATTTTCAGTGTTTTGTAATATTTATCTTTTCACTTTGATA AACCAGAAATGTTTCTAAATCCTAATATTCTTTGCATATATCTAGCTACTCCCTAAATGGTT CCATCCAAGGCTTAGAGTACCCAAAGGCTAAGAAATTCTAAAGAACTGATACAGGAGTAACA ATATGAAGAATTCATTAATATCTCAGTACTTGATAAATCAGAAAGTTATATGTGCAGATTAT TTTCCTTGGCCTTCAAGCTTCCAAAAAACTTGTAATAATCATGTTAGCTATAGCTTGTATAT ACACATAGAGATCAATTTGCCAAATATTCACAATCATGTAGTTCTAGTTTACATGCCAAAGT CTTCCCTTTTTAACATTATAAAAGCTAGGTTGTCTCTTGAATTTTGAGGCCCTAGAGATAGT CTGGCCATACCATAGATTTGGGATGATGTAGTCTGTGCTAAATATTTTGCTGAAGAAGCAGT TTCTCAGACACACATCTCAGAATTTTAATTTTTAGAAATTCATGGGAAATTGGATTTTTGT AATAATCTTTTGATGTTTTAAACATTGGTTCCCTAGTCACCATAGTTACCACTTGTATTTTA AGTCATTTAAACAAGCCACGGTGGGGCTTTTTTCTCCTCAGTTTGAGGAGAAAAATCTTGAT AATTCAAGCTGTGACTATTGTATATCTTTCCAAGAGTTGAAATGCTGGCTTCAGAATCATAC CAGATTGTCAGTGAAGCTGATGCCTAGGAACTTTTAAAGGGATCCTTTCAAAAGGATCACTT AGCAAACACATGTTGACTTTAACTGATGTATGAATATTAATACTCTAAAAATAGAAAGACC AGTAATATAAGTCACTTTACAGTGCTACTTCACACTTAAAAGTGCATGGTATTTTTCATG GTATTTTGCATGCAGCCAGTTAACTCTCGTAGATAGAGAAGTCAGGTGATAGATGATATTAA AAATTAGCAAACAAAAGTGACTTGCTCAGGGTCATGCAGCTGGGTGATGATAGAAGAGTGGG CTTTAACTGGCAGGCCTGTATGTTTACAGACTACCATACTGTAAATATGAGCTTTATGGTGT CATTCTCAGAAACTTATACATTTCTGCTCTCCTTTCTCCTAAGTTTCATGCAGATGAATATA AGGTAATATACTATTATAATTCATTTGTGATATCCACAATAATATGACTGGCAAGAATTG GTGGAAATTTGTAATTAAAATAATTATTAAACCT

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FIGURE 9

MEKQCCSHPVICSLSTMYTFLLGAIFIALSSSRILLVKYSANEENKYDYLPTTVNVCSELVK
LVFCVLVSFCVIKKDHQSRNLKYASWKEFSDFMKWSIPAFLYFLDNLIVFYVLSYLQPAMAV
IFSNFSIITTALLFRIVLKRRLNWIQWASLLTLFLSIVALTAGTKTLQHNLAGRGFHHDAFF
SPSNSCLLFRSECPRKDNCTAKEWTFPEAKWNTTARVFSHIRLGMGHVLIIVQCFISSMANI
YNEKILKEGNQLTESIFIQNSKLYFFGILFNGLTLGLQRSNRDQIKNCGFFYGHSAFSVALI
FVTAFQGLSVAFILKFLDNMFHVLMAQVTTVIITTVSVLVFDFRPSLEFFLEAPSVLLSIFI
YNASKPQVPEYAPRQERIRDLSGNLWERSSGDGEELERLTKPKSDESDEDTF

Transmembrane domains:

amino acids 16-36 (type II), 50-74, 147-168, 229-250, 271-293, 298-318, 328-368

N-glycosylation sites.

amino acids 128-132, 204-208, 218-222, 374-378

Glycosaminoglycan attachment site.

amino acids 402-406

N-myristoylation sites.

amino acids 257-263, 275-281, 280-286, 284-290, 317-323

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FIGURE 10

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FIGURE 11

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGGCCGGCTTGGCTAGCGCGCGGCGCC GTGGCTAAGGCTGCTACGAAGCGAGCTTGGGAGGAGCAGCGGCCTGCGGGGCAGAGGAGCAT CCCGTCTACCAGGTCCCAAGCGGCGTGGCCCGCGGGTCATGGCCAAAGGAGAAGGCGCCGAG AGCGGCTCCGCGGGGGGCTGCTACCCACCAGCATCCTCCAAAGCACTGAACGCCCGGCCCA GGTGAAGAAGAACCGAAAAAGAAGAACAACAGTTGTCTGTTTGCAACAAGCTTTGCTATG CTATTGG**ATG**TGGCTCAGGTGGGCCCTTTCTCTGCCTCCATCATCCTGTTTGTGGGCCGAGC CTGGGATGCCATCACAGACCCCCTGGTGGGCCTCTGCATCAGCAAATCCCCCTGGACCTGCC TGGGTCGCCTTATGCCCTGGATCATCTTCTCCACGCCCCTGGCCGTCATTGCCTACTTCCTC ATCTGGTTCGTGCCCGACTTCCCACACGGCCAGACCTATTGGTACCTGCTTTTCTATTGCCT CTTTGAAACAATGGTCACGTGTTTCCATGTTCCCTACTCGGCTCTCACCATGTTCATCAGCA ACCGAGCAGACTGAGCGGGATTCTGCCACCGCCTATCGGATGACTGTGGAAGTGCTGGGCAC AGTGCTGGGCACGGCGATCCAGGGACAAATCGTGGGCCAAGCAGACACGCCTTGTTTCCAGG ACTTCAATAGCTCTACAGTAGCTTCACAAAGTGCCAACCATACACATGGCACCACTTCACAC AGGGAAACGCAAAAGGCATACCTGCTGGCAGCGGGGGTCATTGTCTGTATCTATATAATCTG TGCTGTCATCCTGATCCTGGGCGTGCGGGAGCAGAGAACCCTATGAAGCCCAGCAGTCTG AGCCAATCGCCTACTTCCGGGGCCTACGGCTGGTCATGAGCCACGGCCCATACATCAAACTT ATTACTGGCTTCCTCTTCACCTCCTTGGCTTTCATGCTGGTGGAGGGGAACTTTGTCTTGTT TTGCACCTACACCTTGGGCTTCCGCAATGAATTCCAGAATCTACTCCTGGCCATCATGCTCT CGGCCACTTTAACCATTCCCATCTGGCAGTGGTTCTTGACCCGGTTTGGCAAGAAGACAGCT GTATATGTTGGGATCTCATCAGCAGTGCCATTTCTCATCTTGGTGGCCCTCATGGAGAGTAA CCTCATCATTACATATGCGGTAGCTGTGGCAGCTGGCATCAGTGTGGCAGCTGCCTTCTTAC TACCCTGGTCCATGCTGCCTGATGTCATTGACGACTTCCATCTGAAGCAGCCCCACTTCCAT GGAACCGAGCCCATCTTCTCCTTCTATGTCTTCTCACCAAGTTTGCCTCTGGAGTGTC ACTGGGCATTTCTACCCTCAGTCTGGACTTTGCAGGGTACCAGACCCGTGGCTGCTCGCAGC CGGAACGTGTCAAGTTTACACTGAACATGCTCGTGACCATGGCTCCCATAGTTCTCATCCTG GGCCCTGCAGGCACTGAGGGACGAGGCCAGCAGCTCTGGCTCCAGAAACAGACTCCACAG AGCTGGCTAGCATCCTC**TAG**GGCCCGCCACGTTGCCCGAAGCCACCATGCAGAAGGCCACAG AAGGGATCAGGACCTGTCTGCCGGCTTGCTGAGCAGCTGCAGGTGCTAGGAAGGGAA CTGAAGACTCAAGGAGGTGGCCCAGGACACTTGCTGTGCTCACTGTGGGGCCGGCTGCTCTG TGGCCTCCTGCCTCTGCCTGCCTGTGGGGCCAAGCCCTGGGGCTGCCACTGTGAATA TTAATGTTATTAATTTTCATAAAAGCTGGAAAGC

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FIGURE 12

MWLRWALSLPPSSCLWAEPGMPSQTPWWASASANPPGPAWVALCPGSSSPRPWPSLPTSSSG
SCPTSHTARPIGTCFSIASLKQWSRVSMFPTRLSPCSSATEQTERDSATAYRMTVEVLGTVL
GTAIQGQIVGQADTPCFQDFNSSTVASQSANHTHGTTSHRETQKAYLLAAGVIVCIYIICAV
ILILGVREQREPYEAQQSEPIAYFRGLRLVMSHGPYIKLITGFLFTSLAFMLVEGNFVLFCT
YTLGFRNEFQNLLLAIMLSATLTIPIWQWFLTRFGKKTAVYVGISSAVPFLILVALMESNLI
ITYAVAVAAGISVAAAFLLPWSMLPDVIDDFHLKQPHFHGTEPIFFSFYVFFTKFASGVSLG
ISTLSLDFAGYQTRGCSQPERVKFTLNMLVTMAPIVLILLGLLLFKMYPIDEERRRQNKKAL
QALRDEASSSGCSETDSTELASIL

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FIGURE 13

GGGAAACGCAAAAGGCATACCTGCTGGCAGCGGGGGTCATTGTCTGTATCTATATAATCTGT
GCTGTCATCCTGATCCTGGGCGTGCGGGAGCAGAGAAACCCTATGAAGCCCAGCAGTCTGA
GCCAATCGCCTACTTCCGGGGCCTACGGCTGGTCATGAGCCACGGCCCATACATCAAACTTA
TTACTGGCTTCCTCTTCACCTCCTTGGCTTTCATGCTGGTGGAGGGGAACTTTGTCTTGTTT
TGCACCTACACCTTGGGCTTCCGCAATGAATTCCAGAATCTACTCCTGGCCATCATGCTCTC
GGCCACTTTAACCATTCCCATCTGGCAGTGGTTCTTGACCCGGTTTGGCAAGAAGACAGCTG
TATATGTTGGGATCTCATCAGCAGTGCCATTTCTCATCTTGGTGGCCCTCATGGAGAGTAAC
CTCATCATTACATATGCGGTAGCTGTGGCAGCTGGCATCAGTGTGGCAGCCCCACTTCCATG
ACCCTGGTCCATGCTGCCTGATGTCATTGACGACTTCCATCTGAAGCAGCCCCACTTCCATG
GAACCGAGCCCAT

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FIGURE 14

GGGGCTTCGGCGCCAGCGCCAGCGCTAGTCGGTCTGGTAAGGATTTACAAAAGGTGCAGGT ATGAGCAGGTCTGAAGACTAACATTTTGTGAAGTTGTAAAACAGAAAACCTGTTAGAA**ATG**T GGTGGTTTCAGCAAGGCCTCAGTTTCCTTCCTTCAGCCCTTGTAATTTGGACATCTGCTGCT TTCATATTTTCATACATTACTGCAGTAACACTCCACCATATAGACCCGGCTTTACCTTATAT CAGTGACACTGGTACAGTAGCTCCAGAAAAATGCTTATTTGGGGCAATGCTAAATATTGCGG CAGTTTTATGCATTGCTACCATTTATGTTCGTTATAAGCAAGTTCATGCTCTGAGTCCTGAA GAGAACGTTATCATCAAATTAAACAAGGCTGGCCTTGTACTTGGAATACTGAGTTGTTTAGG ACTTTCTATTGTGGCAAACTTCCAGAAAACAACCCTTTTTGCTGCACATGTAAGTGGAGCTG TGCTTACCTTTGGTATGGGCTCATTATATATGTTTGTTCAGACCATCCTTTCCTACCAAATG CAGCCCAAAATCCATGGCAAACAAGTCTTCTGGATCAGACTGTTGTTGGTTATCTGGTGTGG AGTAAGTGCACTTAGCATGCTGACTTGCTCATCAGTTTTGCACAGTGGCAATTTTTGGGACTG ATTTAGAACAGAAACTCCATTGGAACCCCGAGGACAAAGGTTATGTGCTTCACATGATCACT ACTGCAGCAGAATGGTCTATGTCATTTTCCTTCTTTGGTTTTTTCCTGACTTACATTCGTGA TTTTCAGAAAATTTCTTTACGGGTGGAAGCCAATTTACATGGATTAACCCTCTATGACACTG CACCTTGCCCTATTAACAATGAACGAACACGGCTACTTTCCAGAGATATT**TGA**TGAAAGGAT AAAATATTTCTGTAATGATTATGATTCTCAGGGGATTGGGGAAAGGTTCACAGAAGTTGCTTA TTCTTCTGAAATTTTCAACCACTTAATCAAGGCTGACAGTAACACTGATGAATGCTGATA ATCAGGAAACATGAAAGAAGCCATTTGATAGATTATTCTAAAGGATATCATCAAGAAGACTA TTAAAAACACCTATGCCTATACTTTTTTATCTCAGAAAATAAAGTCAAAAGACTATG

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FIGURE 15

MWWFQQGLSFLPSALVIWTSAAFIFSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNI
AAVLCIATIYVRYKQVHALSPEENVIIKLNKAGLVLGILSCLGLSIVANFQKTTLFAAHVSG
AVLTFGMGSLYMFVQTILSYQMQPKIHGKQVFWIRLLLVIWCGVSALSMLTCSSVLHSGNFG
TDLEQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGFFLTYIRDFQKISLRVEANLHGLTLYD
TAPCPINNERTRLLSRDI

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FIGURE 16

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FIGURE 17

CCCACGCGTCCGCCGCCGCTGCGTCCCGGAGTGCAAGTGAGCTTCTCGGCTGCCCCGCGGG CCGGGGTGCGGAGCCGATGCGCCCGCTTCTCGGCCTCCTTCTGGTCTTCGCCGGCTGCAC AGGCTGGAGGCAGGTCGCTGTGGTTCCCCTCCGACCTGGCAGAGCTGCGGGAGCTCTCTGAG GTCCTTCGAGAGTACCGGAAGGAGCACCAGGCCTACGTGTTCCTGCTCTTCTGCGGCGCCCTA CCTCTACAAACAGGGCTTTGCCATCCCGGCTCCAGCTTCCTGAATGTTTTAGCTGGTGCCT TGCTACCTGCTCTCCAGTATTTTTGGCAAACAGTTGGTGGTGTCCTACTTTCCTGATAAAGT TGAGACTTTTCCCCATGACACCAAACTGGTTCTTGAACCTCTCGGCCCCAATTCTGAACATT CCCATCGTGCAGTTCTTCTCAGTTCTTATCGGTTTGATCCCATATAATTTCATCTGTGT GCAGACAGGGTCCATCCTGTCAACCCTAACCTCTCTGGATGCTCTTTTCTCCTGGGACACTG TCTTTAAGCTGTTGGCCATTGCCATGGTGGCATTAATTCCTGGAACCCTCATTAAAAAATTT AGTCAGAAACATCTGCAATTGAATGAAACAAGTACTGCTAATCATATACACAGTAGAAAAGA CACATGATCTGGATTTTCTGTTTGCCACATCCCTGGACTCAGTTGCTTATTTGTGTAATGGA TGTGGTCCTCTAAAGCCCCTCATTGTTTTTGATTGCCTTCTATAGGTGATGTGGACACTGTG CATCAATGTGCAGTGTCTTTTCAGAAAGGACACTCTGCTCTTGAAGGTGTATTACATCAGGT TTTCAAACCAGCCCTGGTGTAGCAGACACTGCAACAGATGCCTCCTAGAAAATGCTGTTTGT GGCCGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCCGGTGATTC ACAAGGTCAGGAGTTCAAGACCAGCCTGGCCAAGATGGTGAAATCCTGTCTCTAATAAAAAT ACAAAATTAGCCAGGCGTGGTGGCAGGCACCTGTAATCCCAGCTACTCGGGAGGCTGAGGC AGGAGAATTGCTTGAACCAAGGTGGCAGAGGTTGCAGTAAGCCAAGATCACCACTGCACT CCAGCCTGGGTGATAGAGTGAGACACTGTCTTGAC

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FIGURE 18

MRPLLGLLLVFAGCTFALYLLSTRLPRGRRLGSTEEAGGRSLWFPSDLAELRELSEVLREYR KEHQAYVFLLFCGAYLYKQGFAIPGSSFLNVLAGALFGPWLGLLLCCVLTSVGATCCYLLSS IFGKQLVVSYFPDKVALLQRKVEENRNSLFFFLLFLRLFPMTPNWFLNLSAPILNIPIVQFF FSVLIGLIPYNFICVQTGSILSTLTSLDALFSWDTVFKLLAIAMVALIPGTLIKKFSQKHLQ LNETSTANHIHSRKDT

Important features:

Signal peptide:

amino acids 1-17

Transmembrane domains:

amino acids 101-123, 189-211

N-glycosylation sites.

amino acids 172-176, 250-254

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 240-244, 261-265

N-myristoylation site.

amino acids 13-19, 104-110, 115-121, 204-210

Amidation site.

amino acids 27-31

Prokaryotic membrane lipoprotein lipid attachment site.

amino acids 4-15

Protein splicing proteins.

amino acids 25-31

Sugar transport proteins.

amino acids 162-172

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FIGURE 19

CCGAGGCGGAGGGGCCCGAGGGGGGCCCCGCATGAATCATTGTAGTCAATCATTTT CCAGTTCTCAGCCGCTCAGTTGTGATCAAGGGACACGTGGTTTCCGAACTGCCAGCTCAGAA TAGGAAAATAACTTGGGATTTTATATTGGAAGAC<u>ATG</u>GATCTTGCTGCCAACGAGATCAGCA TCAGAGAAGGCAATTGAAAAATTTATCAGACAGCTGCTGGAAAAGAATGAACCTCAGAGACC CCCCCGCAGTATCCTCTCTTATAGTTGTGTATAAGGTTCTCGCAACCTTGGGATTAATCT TGCTCACTGCCTACTTTGTGATTCAACCTTTCAGCCCATTAGCACCTGAGCCAGTGCTTTCT GGAGCTCACACCTGGCGCTCACTCATCCATCACATTAGGCTGATGTCCTTGCCCATTGCCAA CAGACTTTGACCCCTGGTGGACAAACGACTGTGAGCAGAATGAGTCAGAGCCCATTCCTGCC AACTGCACTGGCTGTGCCCAGAAACACCTGAAGGTGATGCTCCTGGAAGACGCCCCAAGGAA ATTTGAGAGGCTCCATCCACTGGTGATCAAGACGGGAAAGCCCCTGTTGGAGGAAGAGATTC AGCATTTTTTGTGCCAGTACCCTGAGGCGACAGAAGGCTTCTCTGAAGGGTTTTTCGCCAAG TGGTGGCGCTGCTTTCCTGAGCGGTGGTTCCCATTTCCTTATCCATGGAGGAGACCTCTGAA CCTCTTTAAACAAGTGCTCCTTTCTTCACCCAGAACCTGTTGTGGGGAGTAAGATGCATAAG GTGCCGAAGACATTGTCAGTCTGTGGCCATGCCAATAGAGCCAGGGGATATCGGCTATGTCG ACACCACCCACTGGAAGGTCTACGTTATAGCCAGAGGGGTCCAGCCTTTGGTCATCTGCGAT GGAACCGCTTTCTCAGAACTG**TAG**GAAATAGAACTGTGCACAGGAACAGCTTCCAGAGCCGA AAACCAGGTTGAAAGGGGAAAAATAAAAACAAAAACGATGAAACTGCAAAAA

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FIGURE 20

MDLAANEISIYDKLSETV.DLVRQTGHQCGMSEKAIEKFIRQLLEKNEPQRPPPQYPLLIVVY KVLATLGLILLTAYFVIQPFSPLAPEPVLSGAHTWRSLIHHIRLMSLPIAKKYMSENKGVPL HGGDEDRPFPDFDPWWTNDCEQNESEPIPANCTGCAQKHLKVMLLEDAPRKFERLHPLVIKT GKPLLEEEIQHFLCQYPEATEGFSEGFFAKWWRCFPERWFPFPYPWRRPLNRSQMLRELFPV FTHLPFPKDASLNKCSFLHPEPVVGSKMHKMPDLFIIGSGEAMLQLIPPFQCRRHCQSVAMP IEPGDIGYVDTTHWKVYVIARGVQPLVICDGTAFSEL

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FIGURE 21

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FIGURE 22

CACCCGAATGGCGCCACTTCATCGACAAACAGGTACAGCCAACCATGTCCCAGTTCGAAATG CACCCGATGGCGCCACTTCATCGACAACCAGGTACAGCCAACCATGCCCAGTTCGAAATG
GACACGTATGCTAAGAGCCACGACCTTATGTCAGGTTCTGGAATGCCTGCTATGACATGCT
TATGAGCAGTGGGCAGCGGCGCCAGTGGGAGCGCCCCAGAGTCGTCGGGCCTTCCAGGAGC
TGGTGCTGGAACCTGCGCAGAGGCGGCGCCTGGAGGGGCTACGCTACACGGCAGTGCTG
AAGCAGCAGCAACGCAGCACTCCATGGCCTGCACTGGGGGGGCGCTGTGGCGCCAGCT
CGCCAGCCCATGTGGGGCCTTGAGGGACACTCCCATCCCCGCTGGAAACTGTCCA
GCGCCGAGACATATTCACGCATGCGTCTGAAGCTGGTGCCCAACCATCACTTCGACCCTCAC
CTGGAAGCCAGCGCTCTCGAGACCAAAGTGGTGCCCCAACCCCCACCGAGGAGGC
CTCACTGCCTCCGCCACCACCACCACCCCCACCGAGTTGCTGCAGC AGGACCAGCTCGGCGAGGACGAGCTGGCTGAGCTGGAGACCCCGATGGAGGCAGCAGAACTG GATGAGCAGCGTGAGAAGCTGGTGCTGTCGGCCGAGTGCCAGCTGGTGACGGTAGTGGCCGT GGTCCCAGGGCTGCTGGAGGTCACCACACAGAATGTATACTTCTACGATGGCAGCACTGAGC GCTGGAAACCGAGGGTCACCACACAGAATGTATACTTCTACGATGGCAGCACTGAGC
GCGTGGAAACCGAGGGGGCATCGGCTATGATTTCCGGCGCCCACTGGCCCAGCTGCGTGAG
GTCCACCTGCGGCGTTCAACCTGCGCCGTTCAGCACTTGAGCTCTCTTTTATCGATCAGGC
CAACTACTTCCTCAACTTCCCATGCAAGGTGGGCACGACCCCAGTCTCATCTCCTAGCCAGA
CTCCGAGACCCCAGCCTGGCCCCATCCCACCCCATACCCAGGTACGGAACCAGGTGTACTCG
TGGCTCCTGCGCCTACCGCCCCCTCTCAAGGCTACCTAAGCAGCCGCTCCCCCCCAGGAGAT GCTGCGTGCCTCAGGCCTTACCCAGAAATGGGTACAGCGTGAGATATCCAACTTCGAGTACT GGACACCACGTGCATGGTGTGGCGGCTCCTGCATCAGGGTGGTCTGTCAGTAGGCCTGGCAC CAAAGCCTGTGCAGGTCCTGTATGGGCATGGGGCTGCAGTGAGCTGTGTGGCCATCAGCACT GAACTTGACATGGCTGTGTCTGGATCTGAGGATGGAACTGTGATCATACACACTGTACGCCG CGGACAGTTTGTAGCGGCACTACGGCCTCTGGGTGCCACATTCCCTGGACCTATTTTCCACC TGGCATTGGGGTCCGAAGGCCAGATTGTGGTACAGAGCTCAGCGTGGGAACGTCCTGGGGCC GCGGGGCCCACCTGCCCAGCTCAGGGATTGGCGGGCGATGTTACCCCCTCAGGGATTGGCG GGCGGAAGTCCCGCCCTCGCCGGCTGAGGGCCCCCTGAGGGCCAGCACTGGCGTCT

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FIGURE 23

MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLEGL RYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLKLVPN HHFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDELAELETP MEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTONVYFYDGSTERVETEEGIGYDFRRP LAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTPVSSPSOTPRPOPGPIPPHTOV RNQVYSWLLRLRPPSQGYLSSRSPQEMLRASGLTQKWVQREISNFEYLMQLNTIAGRTYNDL SQYPVFPWVLQDYVSPTLDLSNPAVFRDLSKPIGVVNPKHAQLVREKYESFEDPAGTIDKFH YGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFDCSDRQFHSVAAAWQARLESPADVKELIP EFFYFPDFLENQNGFDLGCLQLTNEKVGDVVLPPWASSPEDFIQQHRQALESEYVSAHLHEW IDLI FGYKQRGPAAEEALNVFYYCTYEGAVDLDHVTDERERKALEGI I SNFGQTPCQLLKEP HPTRLSAEEAAHRLARLDTNSPSIFQHLDELKAFFAEVTVSASGLLGTHSWLPYDRNISNYF SFSKDPTMGSHKTQRLLSGPWVPGSGVSGQALAVAPDGKLLFSGGHWDGSLRVTALPRGKLL SQLSCHLDVVTCLALDTCGIYLISGSRDTTCMVWRLLHQGGLSVGLAPKPVQVLYGHGAAVS CVAISTELDMAVSGSEDGTVIIHTVRRGQFVAALRPLGATFPGPIFHLALGSEGOIVVOSSA WERPGAQVTYSLHLYSVNGKLRASLPLAEQPTALTVTEDFVLLGTAQCALHILQLNTLLPAA PPLPMKVAIRSVAVTKERSHVLVGLEDGKLIVVVAGQPSEVRSSQFARKLWRSSRRISQVSS **GETEYNPTEAR**

N-glycosylation site.

amino acids 677-681

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 985-989

Tyrosine kinase phosphorylation site.

amino acids 56-65, 367-376, 543-551

N-myristoylation site.

amino acids 61-67, 436-442, 604-610, 610-616, 664-670, 691-697, 706-712, 711-717, 769-775, 785-791; 802-808, 820-826, 834-840, 873-879, 912-918, 954-960

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FIGURE 24

CACGGCCCACCTTGTGAACTCCTCGTGCCCAGGGCTGATGTGCGTCTTCCAGGGCTACTCAT CCAAAGGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCCTGGGGCTCTTC TGGACCCTTAACTGGGTACTGGCCCTGGGCCAATGCGTCCTCGCTGGAGCCTTTGCCTCCTT CTACTGGGCCTTCCACAAGCCCCAGGACATCCCTACCTTCCCCTTAATCTCTGCCTTCATCC GCACACTCCGTTACCACACTGGGTCATTGGCATTTGGAGCCCTCATCCTGACCCTTGTGCAG ATAGCCCGGGTCATCTTGGAGTATATTGACCACAAGCTCAGAGGAGTGCAGAACCCTGTAGC CCGCTGCATCATGTGCTGTTTCAAGTGCTGCCTCTGGTGTCTGGAAAAATTTATCAAGTTCC TAAACCGCAATGCATACATCATGATCGCCATCTACGGGAAGAATTTCTGTGTCTCAGCCAAA AATGCGTTCATGCTACTCATGCGAAACATTGTCAGGGTGGTCGTCCTGGACAAAGTCACAGA CCTGCTGCTGTTCTTTGGGAAGCTGCTGGTGGTGGTGGGGGGTGCGGGGGTCCTGTCTTTTT TTTTCTCCGGTCGCATCCCGGGGCTGGGTAAAGACTTTAAGAGCCCCCACCTCAACTATTAC TGGCTGCCCATCATGACCTCCATCCTGGGGGCCTATGTCATCGCCAGCGGCTTCTTCAGCGT TTTCGGCATGTGTGGACACGCTCTTCCTCTGCTTCCTGGAAGACCTGGAGCGGAACAACG GCTCCCTGGACCGGCCCTACTACATGTCCAAGAGCCTTCTAAAGATTCTGGGCAAGAAGAAC GAGGCGCCCCGGACAACAAGAAGAGGAAGAAGTGACAGCTCCGGCCCTGATCCAGGACTGC ACCCCACCCCACCGTCCAGCCATCCAACCTCACTTCGCCTTACAGGTCTCCATTTTGTGGT AAAAAAAGGTTTTAGGCCAGGCGCCGTGGCTCACGCCTGTAATCCAACACTTTGAGAGGCTG AGGCGGGCGGATCACCTGAGTCAGGAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTCC GTCTCTATTAAAAATACAAAAATTAGCCGAGAGTGGTGGCATGCACCTGTCATCCCAGCTAC TCGGGAGGCTGAGCCAGGAGAATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCGAGA AAAGATTTTATTAAAGATATTTTGTTAACTC

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FIGURE 25

RTRGRTRGGCEKVPINTSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLGLF
WTLNWVLALGQCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGALILTLVQ
IARVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNFCVSAK
NAFMLLMRNIVRVVVLDKVTDLLLFFGKLLVVGGVGVLSFFFFSGRIPGLGKDFKSPHLNYY
WLPIMTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSLDRPYYMSKSLLKILGKKN
EAPPDNKKRKK

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FIGURE 26

GAGTCTTGACCGCCGCGGGCTCTTGGTACCTCAGCGCGAGCGCCAGGCGTCCGGCCGCGT GGCT**ATG**TTCGTGTCCGATTTCCGCAAAGAGTTCTACGAGGTGGTCCAGAGCCAGAGGGTCC CAGTGTGACCACGTGCAATATACGCTGGTTCCAGTTTCTGGGTGGCAAGAACTTGAAACTGC ATTTCTTGAGCATAAAGAACAGTTTCATTATTTTATTCTCATAAACTGTGGAGCTAATGTAG CCAGTCAATGTCGTCAATGTATACAACGATACCCAGATCAAATTACTCATTAAACAAGATGA TGACCTTGAAGTTCCCGCCTATGAAGACATCTTCAGGGATGAAGAGGAGGATGAAGAGCATT CAGGAAATGACAGTGATGGGTCAGAGCCTTCTGAGAAGCGCACACGGTTAGAAGAGGAGATA GTGGAGCAAACCATGCGGAGGGGGGCGGCGAGAGTGGGAGGCCCGGAGAAGAGACATCCT CTTTGACTACGAGCAGTATGAATATCATGGGACATCGTCAGCCATGGTGATGTTTGAGCTGG CTTGGATGCTGTCCAAGGACCTGAATGACATGCTGTGGTGGGCCATCGTTGGACTAACAGAC CAGTGGGTGCAAGACAAGATCACTCAAATGAAATACGTGACTGATGTTGGTGTCCTGCAGCG CCACGTTTCCCGCCACAACCACCGGAACGAGGATGAGGAGAACACTCTCCGTGGACTGCA CACGGATCTCCTTTGAGTATGACCTCCGCCTGGTGCTCTACCAGCACTGGTCCCTCCATGAC AGCCTGTGCAACACCAGCTATACCGCAGCCAGGTTCAAGCTGTGGTCTGTGCATGGACAGAA GCGGCTCCAGGAGTTCCTTGCAGACATGGGTCTTCCCCTGAAGCAGGTGAAGCAGAAGTTCC AGGCCATGGACATCTCCTTGAAGGAGAATTTGCGGGAAATGATTGAAGAGTCTGCAAATAAA TCTGGCCAGCGACGTGTCTTTGCCACCATGTCTTTGATGGAGAGCCCCGAGAAGGATGGCT CAGGGACAGATCACTTCATCCAGGCTCTGGACAGCCTCTCCAGGAGTAACCTGGACAAGCTG TACCATGGCCTGGAACTCGCCAAGAAGCAGCTGCGAGCCACCCAGCAGACCATTGCCAGCTGC CTTTGCACCAACCTCGTCATCTCCCAGGGGCCTTTCCTGTACTGCTCTCTCATGGAGGGCAC TCCAGATGTCATGCTGTTCTCTAGGCCGGCATCCCTAAGCCTGCTCAGCAAACACCTGCTCA AGTCCTTTGTGTGTCGACAAGAACCGGCGCTGCAAACTGCTGCCCCTGGTGATGGCTGCC CCCCTGAGCATGGAGCATGGCACAGTGACCGTGGTGGGCATCCCCCCAGAGACCGACAGCTC GGACAGGAAGACTTTTTTGGGAGGGCGTTTGAGAAGGCAGCGGAAAGCACCAGCTCCCGGA TGCTGCACAACCATTTTGACCTCTCAGTAATTGAGCTGAAAGCTGAGGATCGGAGCAAGTTT CTGGACGCACTTATTTCCCTCCTGTCCTAGGAATTTGATTCTTCCAGAATGACCTTCTTATT TATGTAACTGGCTTTCATTTAGATTGTAAGTTATGGACATGATTTGAGATGTAGAAGCCATT TTTTATTAAATAAAATGCTTATTTTAGGAAA

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FIGURE 27

MFVSDFRKEFYEVVQSQRVLLFVASDVDALCACKILQALFQCDHVQYTLVPVSGWQELETAF
LEHKEQFHYFILINCGANVDLLDILQPDEDTIFFVCDSHRPVNVVNVYNDTQIKLLIKQDDD
LEVPAYEDIFRDEEEDEEHSGNDSDGSEPSEKRTRLEEEIVEQTMRRRQRREWEARRRDILF
DYEQYEYHGTSSAMVMFELAWMLSKDLNDMLWWAIVGLTDQWVQDKITQMKYVTDVGVLQRH
VSRHNHRNEDEENTLSVDCTRISFEYDLRLVLYQHWSLHDSLCNTSYTAARFKLWSVHGQKR
LQEFLADMGLPLKQVKQKFQAMDISLKENLREMIEESANKFGMKDMRVQTFSIHFGFKHKFL
ASDVVFATMSLMESPEKDGSGTDHFIQALDSLSRSNLDKLYHGLELAKKQLRATQQTIASCL
CTNLVISQGPFLYCSLMEGTPDVMLFSRPASLSLLSKHLLKSFVCSTKNRRCKLLPLVMAAP
LSMEHGTVTVVGIPPETDSSDRKNFFGRAFEKAAESTSSRMLHNHFDLSVIELKAEDRSKFL
DALISLLS

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FIGURE 28

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FIGURE 29

CAGGAACCCTCTCTTTGGGTCTGGATTGGGACCCCTTTCCAGTACCATTTTTTCTAGTGAACCCGAAGGGACGATACCAGAAAACACCCTCAACCCAAAGGAAATAGACTACAGCCCCAATTG GAGTAAAGTACGCTCCGGTCACC<u>ATC</u>GTGACAGCCGCCCTGGGTCCCGTCTGGGCAGCGCTC CAGTAAAGTACGCTCCGGTCACCATGGTGACAGCCGCCCTGGGTCCCGTCTGGGCAGCGCTC
CTGCTCTTTCTCCTGATGTGTAGATCCGTATGGTGAGCTCACCTTTGACAGAGCTGTGGC
CAGCGGCTGCCAACGGTGCTGTGACTCTGAGGACCCCTGGATCCTGCCATGTATCCTCAG
CCTCTTCCTCCGGCCGCCCCACGCCCTGCCTGAGATCAGACCCTACATTAATATCACCATC
CTGAAGGGTGACAAAGGGGACCCAGGCCCAATGGGCCTGCCAGGGTACATGGGCAGGAGGG
TCCCCAAGGGGAGCCTTGCCCCTAGGGCAGCAAGGGGGAGATGGGCAGCCCCG
GCGCCCCGTGCCAGAAGCGCTTCTTCGCAAAGGGTCTTTTGTAACCTTTGATGGGTCCTTTGA
CATGGCGACAGCCGCACTTTATTCCATACTTCTTCAGCCTCATTTTTCCATACCACAAAAGGGTCTTTTTC ACAGCTGGAATTACAAGGAGACGTACGTGCACATTATGCATAACCAGAAAGAGGCTGTCATC CTGTACGCGCAGCCAGCGAGCGCAGCATCATGCAGAGCCAGAGTGTGATGCTGGACCTGGCCTACGGGGACCGCGTCTGGGTGCGGCTCTTCAAGCGCCAGCGCGAGAACGCCATCTACAGCA ACCCAGGAGTGTGGGGGCATTTGGGGGGTGAAGTGGCCCCCGAAGAATGGAACCCACACCCA
TAGCTCTCCCACAGCTGATACGGCATCCTGCGAGAAGACCTGCCCTCCACTGGGATCCC
CTTCCTGCCTCCCCAGGGCCTCCAGGGCCTTGCTCAGTCCCTTCCACCAAAGTCATCT
GAACTTCCGTTTCCCCAGGGCCTCCAGCTGCCCTCAGACACTGATGTCTGCCCAGGTGCT
CTCTGCCCCTCATGCCCTCTCACCGGCCCAGTGCCCCGACTCTCCAGGCTTTATCAAGGTG
CTAAGGCCCGGGTGGGCACCTCCTCGTCTCAGAGCCCTCCTCCGGCCTTGTTCCCCTTTAC

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FIGURE 30

MVTAALGPVWAALLLFLLMCEIRMVELTFDRAVASGCQRCCDSEDPLDPAHVSSASSSGRPH
ALPEIRPYINITILKGDKGDPGPMGLPGYMGREGPQGEPGPQGSKGDKGEMGSPGAPCQKRF
FAFSVGRKTALHSGEDFQTLLFERVFVNLDGCFDMATGQFAAPLRGIYFFSLNVHSWNYKET
YVHIMHNQKEAVILYAQPSERSIMQSQSVMLDLAYGDRVWVRLFKRQRENAIYSNDFDTYIT
FSGHLIKAEDD

Important features:

Signal peptide:

amino acids 1-20

N-glycosylation site.

amino acids 72-75

Clq domain proteins.

amino acids 144-178, 78-111 and 84-117

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FIGURE 31

ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCTCGGGCCCGACCCGCCAGGAAAGACTG AGGCCGCGGCCTGCCCGGCTCCCTGCGCCGCCGCCGCCTCCCGGGACAGAAGATCTG CTCCAGGGTCCCTCTGCTGCTGCCGCTGCTGCTACTGGCCCTGGGGCCTGGGGTGCAGG GCTGCCCATCCGGCTGCCAGTGCAGCCACCACAGACTCTTCTGCACTGCCCGCCAGGGG ACCACGGTGCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTGAGAACGGCAT CACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCCTGGACCTGTCAC AGAACCAGATCGCCAGCCTGCCCAGCGGGGTCTTCCAGCCACTCGCCAACCTCAGCAACCTG GACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCCGTGGCCTGCGGCGCCT CGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGCCTGGTGCCTTCGACACGC TCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGCGGGCACTGCCCCCGCTGCGC CTGCCCGCCTGCTGCTGGACCTCAGCCACAACAGCCTCCTGGCCCTGGAGCCCGGCAT CCTGGACACTGCCAACGTGGAGGCGCTGCGCTGGTCTGGGGCTGCAGCAGCTGGACG AGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACCTGGATGTGTCCGACAACCAGCTGGAG CGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCCTGACGCGCCTGCGGCTGGCCGGCAACAC CCGCATTGCCCAGCTGCGGCCGAGGACCTGGCCGGCCTGGCTGCCCTGCAGGAGCTGGATG TGAGCAACCTAAGCCTGCAGGCCCTGCCTGGCGACCTCTCGGGCCTCTTCCCCCGCCTGCGG CTGCTGGCAGCTGCCCGCAACCCCTTCAACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCTG GGTGCGCGAGAGCCACGTCACACTGGCCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCA AGAACGCTGGCCGGCTGCTCCTGGAGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACC ACCACAGCCACAGTGCCCACCACGAGGCCCGTGGTGCGGGAGCCCACAGCCTTGTCTTCTAG CTGCCCACCGACTGTAGGGCCTGTCCCCCAGCCCCAGGACTGCCCACCGTCCACCTGCCTC AATGGGGGCACATGCCACCTGGGGACACGGCACCACCTGGCGTGCTTGTGCCCCGAAGGCTT CACGGGCCTGTACTGTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCA CGCCGAGGCCACCACGGTCCCTGACCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGC GTGGGGCTGCAGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTA AGTACACGGTCACCCAGCTGCGGCCCAACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGG CCCGGCGGGTGCCGGAGGGCGAGGGCCTGCGGGGAGGCCCATACACCCCCAGCCGTCCA CTCCAACCACGCCCAGTCACCCAGGCCCGCGAGGGCAACCTGCCGCTCCTCATTGCGCCCG CCCTGGCCGCGGTGCTCCTGGCCGCGCTGCGGTGGGGGCAGCCTACTGTGTGCGGCGG GGGCGGCCATGCCACCACCGCTCAGGACAAAGGGCAGGTGGGCCCAGGGGCTGGGCCCCT GGAACTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCGAAGGCAACAGAGGCGGTGGAG AGGCCCTGCCCAGCGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCCAGGGCCTGGCCTC GGCTCTCAGCCAGTGAGATGGCCAGCCCCTCCTGCTGCCACACCACGTAAGTTCTCAGTCC CAACCTCGGGGATGTGCAGACAGGGCTGTGTGACCACAGCTGGGCCCTGTTCCCTCTGGA CCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCCCTAACGTCCCCAGAAC CGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTGCAGTCCCTGGGCACGGCG GGCCCTGCCATGTGCTGGTAACGCATGCCTGGGTCCTGCTGGGCTCTCCCACTCCAGGCGGA CCCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAGGGAGAGCGGGTAGGCGGCTGTG TGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAAGAAACTGGAAAGGAAGATGCTTTA GGAACATGTTTTGCTTTTTTAAAATATATATTTTATAAGAGATCCTTTCCCATTTATTCTG GGAAGATGTTTTCAAACTCAGAGACAAGGACTTTGGTTTTTGTAAGACAAACGATGATATG AAGGCCTTTTGTAAGAAAAAATAAAAGATGAAGTGTGAAA

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FIGURE 32

MCSRVPLLLPLLLLALGPGVQGCPSGCQCSQPQTVFCTARQGTTVPRDVPPDTVGLYVFEN
GITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETFRGLR
RLERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNSLLALEP
GILDTANVEALRLAGLGLQQLDEGLFSRLRNLHDLDVSDNQLERVPPVIRGLRGLTRLRLAG
NTRIAQLRPEDLAGLAALQELDVSNLSLQALPGDLSGLFPRLRLLAAARNPFNCVCPLSWFG
PWVRESHVTLASPEETRCHFPPKNAGRLLLELDYADFGCPATTTTATVPTTRPVVREPTALS
SSLAPTWLSPTAPATEAPSPPSTAPPTVGPVPQPQDCPPSTCLNGGTCHLGTRHHLACLCPE
GFTGLYCESQMGQGTRPSPTPVTPRPPRSLTLGIEPVSPTSLRVGLQRYLQGSSVQLRSLRL
TYRNLSGPDKRLVTLRLPASLAEYTVTQLRPNATYSVCVMPLGPGRVPEGEEACGEAHTPPA
VHSNHAPVTQAREGNLPLLIAPALAAVLLAALAAVGAAYCVRRGRAMAAAAQDKGQVGPGAG
PLELEGVKVPLEPGPKATEGGGEALPSGSECEVPLMGFPGPGLQSPLHAKPYI

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FIGURE 33

GAATCATCCACGCACCTGCAGCTCTGCTGAGAGAGTGCAAGCCGTGGGGGTTTTGAGCTCAT CTTCATCATTCATATGAGGAAATAAGTGGTAAAATCCTTGGAAATACAATGAGACTCATCAG AAACATTTACATATTTTGTAGTATTGTTATGACAGCAGAGGGTGATGCTCCAGAGCTGCCAGAAAAAGGAAAGGAACTGATGACCAACTGCTCCAACATGTCTCTAAGAAAGGTTCCCGCAGACTTG ACAGGATAAAATCTATTTGCTTTTGACCAAAATGGACATAGAAAACCTGACAATATCAAATG CACAAATGCCACACATGCTTTTCCCGAATTATCCTACGAAATTCCAATATTTAAATTTTGCC AATAATATCTTAACAGACGAGTTGTTTAAAAGAACTATCCAACTGCCTCACTTGAAAACTCT CATTTTGAATGCCAATAAACTGGAGACACTTTCTTTAGTAAGTTGCTTTGCTAACAACACAC CCTTGGAACACTTGGATCTGAGTCAAAATCTATTACAACATAAAAATGATGAAAATTGCTCA TGGCCAGAAACTGTGGTCAATATGAATCTGTCATACAATAAATTGTCTGATTCTGTCTTCAG GTGCTTGCCCAAAAGTATTCAAATACTTGACCTAAATAATAACCAAATCCAAACTGTACCTA AAGAGACTATTCATCTGATGGCCTTACGAGAACTAAATATTGCATTTAATTTTCTAACTGAT GTTAAAAGACGTTCATCTCCACGAATTATCTTGCAACACAGCTCTGTTGATTGTCACCATTG TGGTTATTATGCTAGTTCTGGGGTTGGCTGTGGCCTTCTGCTGTCTCCACTTTGATCTGCCC TGGTATCTCAGGATGCTAGGTCAATGCACAAACATGGCACAGGGTTAGGAAAACAACCCA TTACTGGAACCCATTCCATTCTATTGCATTCCCACCAGGTATCATAAACTGAAAGCTCTCCT GGAAAAAAAGCATACTTGGAATGGCCCAAGGATAGGCGTAAATGTGGGCTTTTCTGGGCAA ACCTTCGAGCTGCTATTAATGTTAATGTATTAGCCACCAGAGAAATGTATGAACTGCAGACA TTCACAGAGTTAAATGAAGAGTCTCGAGGTTCTACAATCTCTCTGATGAGAACAGATTGTCT ATAAATCCCACAGTCCTTGGGAAGTTGGGGACCACATACACTGTTGGGATGTACATTGATA ATCTGTATTTCTTTTATAAGTAGAAAAAAAAAAAAAGATAGTTTTTACAGCCT

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FIGURE 34

MRLIRNIYIFCSIVMTAEGDAPELPEERELMTNCSNMSLRKVPADLTPATTTLDLSYNLLFQ
LQSSDFHSVSKLRVLILCHNRIQQLDLKTFEFNKELRYLDLSNNRLKSVTWYLLAGLRYLDL
SFNDFDTMPICEEAGNMSHLEILGLSGAKIQKSDFQKIAHLHLNTVFLGFRTLPHYEEGSLP
ILNTTKLHIVLPMDTNFWVLLRDGIKTSKILEMTNIDGKSQFVSYEMQRNLSLENAKTSVLL
LNKVDLLWDDLFLILQFVWHTSVEHFQIRNVTFGGKAYLDHNSFDYSNTVMRTIKLEHVHFR
VFYIQQDKIYLLTKMDIENLTISNAQMPHMLFPNYPTKFQYLNFANNILTDELFKRTIQLP
HLKTLILNGNKLETLSLVSCFANNTPLEHLDLSQNLLQHKNDENCSWPETVVNMNLSYNKLS
DSVFRCLPKSIQILDLNNNQIQTVPKETIHLMALRELNIAFNFLTDLPGCSHFSRLSVLNIE
MNFILSPSLDFVQSCQEVKTLNAGRNPFRCTCELKNFIQLETYSEVMMVGWSDSYTCEYPLN
LRGTRLKDVHLHELSCNTALLIVTIVVIMLVLGLAVAFCCLHFDLPWYLRMLGQCTQTWHRV
RKTTQEQLKRNVRFHAFISYSEHDSLWVKNELIPNLEKEDGSILICLYESYFDPGKSISENI
VSFIEKSYKSIFVLSPNFVQNEWCHYEFYFAHHNLFHENSDHIILILLEPIPFYCIPTRYHK
LKALLEKKAYLEWPKDRRKCGLFWANLRAAINVNVLATREMYELQTFTELNEESRGSTISLM
RTDCL

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FIGURE 35

GGGGGCTTTCTTGGGCTTGGCTTGGAACACCTGCCTCCAAGGACCGGCCTCGGAGGGGTCGCCGGGAAAGG GAGGGAAGAAGGAAGGGCGGGCCGCCCCCTGCGCCCCCGCGCCCTCTGCGCCCCCTGTCCGCCCCGGC CTGGCAGTGACCCTGGCCGGGGTCGGAGCCCAGGGCGCAGCCCTCGAGGACCCTGATTATTACGGGCAGGAGAT AAGAGGGAGAAGTCGGCTCCGGAGCCGCCTCCACCAGGTAAACACAGCAACAAAAAAGTTATGAGAACCAAGAG TTGGTCTGGAAACCTTAAAAATCACAGACTTCCAGCTCCATGCCTCCACGGTGAAGCGCTATGGCCTGGGGGCA CATCGAGGGAGACTCAACATCCAGGCGGGCATTAATGAAAATGATTTTTATGACGGAGCGTGGTGCGCGGGAAG AAATGACCTCCAGCAGTGGATTGAAGTGGATGCTCGGCGCCTGACCAGATTCACTGGTGTCATCACTCAAGGGA GGAACTCCCTCTGGCTGACTGGCTGACATCCTATAAGGTCATGGTGAGCAATGACAGCCACACGTGGGTC ACTGTTAAGAATGGATCTGGAGACATGATATTTGAGGGAAACAGTGAGAAGGAGATCCCTGTTCTCAATGAGCT ACCCGTCCCCATGGTGGCCCGCTACATCCGCATAAACCCTCAGTCCTGGTTTGATAATGGGAGCATCTGCATGA GAATGGAGATCCTGGGCTGCCCACTGCCAGATCCTAATAATTATTATCACCGCCGGAACGAGATGACCACCACT CAATATCACCAGAATTTACAACATTGGAAAAAGCCACCAGGGCCTGAAGCTGTATGCTGTGGAGATCTCAGATC ACCCTGGGGAGCATGAAGTCGGTGAGCCCGAGTTCCACTACATCGCGGGGGCCCACGGCAATGAGGTGCTGGGC $\tt CGGGAGCTGCTGCTGCTGCTGCTGCTGTTCGTGTCAGGAGTACTTGGCCCGGAATGCGCGCATCGTCCACCT$ GGTGGAGGAGACGCGGATTCACGTCCTCCCCTCAACCCCGATGGCTACGAGAAGGCCTACGAAGGGGGCT CGGAGCTGGGAGGCTGGTCCCTGGGACGCTGGACCCACGATGGAATTGACATCAACAACAACTTTCCTGATTTA AACACGCTGCTCTGGGAGGCAGAGGATCGACAGAATGTCCCCAGGAAAGTTCCCAATCACTATATTGCAATCCC CTTTTGTGCTGGGCGCAACCTGCAGGGCGGCGAGCTGGTGGCGTATCCCTACGACCTGGTGCGGTCCCCC ACACCGCCTCATGACAGACGCCCGGAGGAGGGTGTGCCACACGGAGGACTTCCAGAAGGAGGAGGGCACTGTCA ATGGGGCCTCCTGGCACACCGTCGCTGGAAGTCTGAACGATTTCAGCTACCTTCATACAAACTGCTTCGAACTG TCCATCTACGTGGGCTGTGATAAATACCCACATGAGAGCCAGCTGCCCGAGGAGTGGGAATAACCGGGAATC TCTGATCGTGTTCATGGAGCAGGTTCATCGTGGCATTAAAGGCTTGGTGAGAGATTCACATGGAAAAGGAATCC CAAACGCCATTATCTCCGTAGAAGGCATTAACCATGACATCCGAACAGCCAACGATGGGGGATTACTGGCGCCTC CTGAACCCTGGAGAGTATGTGGTCACAGCAAAGGCCGAAGGTTTCACTGCATCCACCAAGAACTGTATGGTTGG CTATGACATGGGGGCCACAAGGTGTGACTTCACACTTAGCAAAACCAACATGGCCAGGATCCGAGAGATCATGG TGGACTCACTCACTGTTGTTTCCTCTGTAATTCAAGAAGTGCCTGGAAGAGAGGGTGCATTGTGAGGCAGGTCC GAGCCTGTCCGTTCAGAGCCTCTGGCTGCATAGAAAAGGATTCTGGTGCTTCCCCTGTTTGCGTGGCAGCAAGG GTTCCACGTGCATTTGCAATTTGCACAGCTAAAATTGCAGCATTTCCCCAGCTGGGCTGTCCCAAATGTTACCA TTTGAGATGCTCCCAGGCGTCCTAAGAGAATCCACCCTCTCTGGCCCTGGGACATTGCAAGCTGCTACAAATAA ATTCTGTGTTCTTTTGACAATAGCGTCATTGCCAAGTGCACATCAGTGAGCCTCTTGAATCTGTTTAGTCTCCT TGGAGCTTCTTGCACAAATTCTGGGTCCATAAACAACCCCCAAAGTCCCTGATCCAGTAGCCCTGGAGGTT ${\tt CCCCAGGTAGGGAGAGCCAGAGGTGCCAGCCTTCCTGAAGGGCCAGAAAATTTAGCCTGGATCTCCTCTTTTAC}$ GAATTGAGTGCTCATGGGTTGGCCTCATATCAGCCTGGGAGTTATTTTTGATATGTAGAATGCCAGATCTTCCA GATTAGGCTAAATGTAATGAAAACCTCTTAGGATTATCTGTGGAGCATCAGTTTGGGAAGAATTATTGAATTAT

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FIGURE 36

MSRPGTATPALALVLLAVTLAGVGAQGAALEDPDYYGQEIWSREPYYARPEPELETFSPPLP
AGPGEEWERRPQEPRPPKRATKPKKAPKREKSAPEPPPPGKHSNKKVMRTKSSEKAANDDHS
VRVAREDVRESCPPLGLETLKITDFQLHASTVKRYGLGAHRGRLNIQAGINENDFYDGAWCA
GRNDLQQWIEVDARRLTRFTGVITQGRNSLWLSDWVTSYKVMVSNDSHTWVTVKNGSGDMIF
EGNSEKEIPVLNELPVPMVARYIRINPQSWFDNGSICMRMEILGCPLPDPNNYYHRRNEMTT
TDDLDFKHHNYKEMRQLMKVVNEMCPNITRIYNIGKSHQGLKLYAVEISDHPGEHEVGEPEF
HYIAGAHGNEVLGRELLLLLVQFVCQEYLARNARIVHLVEETRIHVLPSLNPDGYEKAYEGG
SELGGWSLGRWTHDGIDINNNFPDLNTLLWEAEDRQNVPRKVPNHYIAIPEWFLSENATVAA
ETRAVIAWMEKIPFVLGGNLQGGELVVAYPYDLVRSPWKTQEHTPTPDDHVFRWLAYSYAST
HRLMTDARRRVCHTEDFQKEEGTVNGASWHTVAGSLNDFSYLHTNCFELSIYVGCDKYPHES
QLPEEWENNRESLIVFMEQVHRGIKGLVRDSHGKGIPNAIISVEGINHDIRTANDGDYWRLL
NPGEYVVTAKAEGFTASTKNCMVGYDMGATRCDFTLSKTNMARIREIMEKFGKQPVSLPARR
LKLRGRKRRQRG

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FIGURE 37

CTAAGAGGACAAGATGAGGCCCGGCCTCTCATTTCTCCTAGCCCTTCTGTTCTTCCTTGGCCAAGCTGCAGGGG ATTTGGGGGATGTGGGACCTCCAATTCCCAGCCCCGGCTTCAGCTCTTTCCCAGGTGTTGACTCCAGCTCCAGC TTCAGCTCCAGCTCCAGGTCGGCTCCAGCTCCAGCCGCAGCTTAGGCAGCGGAGGTTCTGTGTCCCAGTTGTT TTCCAATTTCACCGGCTCCGTGGATGACCGTGGGACCTGCCAGTGCTCTGTTTCCCTGCCAGACACCACCTTTC GTGAGGGAATATGTCCAATTAATTAGTGTGTATGAAAAGAAACTGTTAAACCTAACTGTCCGAATTGACATCAT GGAGAAGGATACCATTTCTTACACTGAACTGGACTTCGAGCTGATCAAGGTAGAAGTGAAGGAGATGGAAAAAC TGGTCATACAGCTGAAGGAGAGTTTTGGTGGAAGCTCAGAAATTGTTGACCAGCTGGAGGTGGAGATAAGAAAT ATGACTCTTTGGTAGAGAAGCTTGAGACACTAGACAAAAACAATGTCCTTGCCATTCGCCGAGAAATCGTGGC CAGGGAGCTGTGGTCATGGTGGTGTGAACATCAGCAAACCGTCTGTGGTTCAGCTCAACTGGAGAGGGTTT ATTGAATACAGATGGGAGACTGTTGGAGTATTATAGACTGTACAACACACTGGATGATTTGCTATTGTATATAA ATGCTCGAGAGTTGCGGATCACCTATGGCCAAGGTAGTGGTACAGCAGTTTACAACAACAACATGTACGTCAAC ATGTACAACACCGGGAATATTGCCAGAGTTAACCTGACCACCAACACGATTGCTGTGACTCAAACTCTCCCTAA TGCTGCCTATAATAACCGCTTTTCATATGCTAATGTTGCTTGGCAAGATATTGACTTTGCTGTGGATGAGAATG GATTGTGGGTTATTTATTCAACTGAAGCCAGCACTGGTAACATGGTGATTAGTAAACTCAATGACACCACACTT ${\tt CAGGTGCTAAACACTTGGTATACCAAGCAGTATAAACCATCTGCTTCTAACGCCTTCATGGTATGTGGGGTTCT}$ GTATGCCACCCGTACTATGAACACCAGAACAGAAGAGATTTTTTACTATTATGACACAAACACAGGGAAAGAGG GCAAACTAGACATTGTAATGCATAAGATGCAGGAAAAAGTGCAGAGCATTAACTATAACCCTTTTGACCAGAAA CTTTATGTCTATAACGATGGTTACCTTCTGAATTATGATCTTTCTGTCTTGCAGAAGCCCCAG<u>TAA</u>GCTGTTTA CTAAAAGTGTGTTCATTTTGCAGCAATGTTTAGGTGCATAGTTCTACCACACTAGAGATCTAGGACATTTGTCT TTGTCAGAGGTCTAGGGGCACTGTGGGCCTAGTGAAGCCTACTGTGAGGAGGCTTCACTAGAAGCCTTAAATTA GGAATTAAGGAACTTAAAACTCAGTATGGCGTCTAGGGGATTCTTTGTACAGGAAATATTGCCCAATGACTAGTC GGAGCTCCTCGAGGGACCAAATCTCCAACTTTTTTTCCCCTCACTAGCACCTGGAATGATGCTTTGTATGTGG CAGATAAGTAAATTTGGCATGCTTATATATTCTACATCTGTAAAGTGCTGAGTTTTATGGAGAGAGGCCTTTTT AACCAGACTTACTAACCAATTCCACCCCCCACCAACCCCTTCTACTGCCTACTTTAAAAAAATTAATAGTTTT AGACTATAAGAAAATCTGATGGCAGTGACAAAGTGCTAGCATTTATTGTTATCTAATAAAGACCTTGGAGCATA TGTGCAACTTATGAGTGTATCAGTTGTTGCATGTAATTTTTGCCTTTGTTTAAGCCTGGAACTTGTAAGAAAAT GAAAATTTAATTTTTTTTTTTCTAGGACGAGCTATAGAAAAGCTATTGAGAGTATCTAGTTAATCAGTGCAGTAGT TGGAAACCTTGCTGGTGTATGTGATGTGCTTCTGTGCTTTTGAATGACTTTATCATCTAGTCTTTGTCTATTTT

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FIGURE 38

MRPGLSFLLALLFFLGQAAGDLGDVGPPIPSPGFSSFPGVDSSSSFSSSSRSGSSSSRSLGS
GGSVSQLFSNFTGSVDDRGTCQCSVSLPDTTFPVDRVERLEFTAHVLSQKFEKELSKVREYV
QLISVYEKKLLNLTVRIDIMEKDTISYTELDFELIKVEVKEMEKLVIQLKESFGGSSEIVDQ
LEVEIRNMTLLVEKLETLDKNNVLAIRREIVALKTKLKECEASKDQNTPVVHPPPTPGSCGH
GGVVNISKPSVVQLNWRGFSYLYGAWGRDYSPQHPNKGLYWVAPLNTDGRLLEYYRLYNTLD
DLLLYINARELRITYGQGSGTAVYNNNMYVNMYNTGNIARVNLTTNTIAVTQTLPNAAYNNR
FSYANVAWQDIDFAVDENGLWVIYSTEASTGNMVISKLNDTTLQVLNTWYTKQYKPSASNAF
MVCGVLYATRTMNTRTEEIFYYYDTNTGKEGKLDIVMHKMQEKVQSINYNPFDQKLYVYNDG
YLLNYDLSVLQKPQ

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FIGURE 39

GCTCTGAAGACCAAGCTGAAAGAGTGTGAGGCCTCTAAAGATCAAACACCCCTGTCGTCCAC
CCTCCTCCCACTCCAGGGAGCTGTGGTCATGGTGGTGGTGAACATCAGCAAACCGTCTGT
GGTTCAGCTCAACTGGAGAGGGTTTTCTTATCTATATGGTGCTTGGGGTAGGGATTACTCTC
CCCAGCATCCAAACAAAGGNATGTATTGGGNGGCGCCATTGAATACAGATGGGAGACTGTTG
GAGTATTATAGACTGTACAACCCACTGGATGATTTGCTATTGTATATAAATGCTCGAGAGTT
GCGGATCACCTATGGCCAAGGTAGTGGTACAGCAGTTTACAACAACAACATGTACGTCAACA
TGTACAACACCGGGNATATTGCCAGAGTTAACCTGACC

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FIGURE 40

AGAAAGGTGTTGTCCCTTGTAACATTTTGGTTGGCTATAAAGCTGTATATCGTTTGTGCTTT GGTTTGGCTATGTTCTATCTTCTCTCTTTTACTAATGATCAAAGTGAAGAGTAGCAGTGA TCCTAGAGCTGCAGTGCACAATGGATTTTGGTTCTTTAAATTTGCTGCAGCAATTGCAATTA TTATTGGGGCATTCTTCATTCCAGAAGGAACTTTTACAACTGTGTGGTTTTATGTAGGCATG TATCAGCTACAGCTCTGAATTATCTGCTGTCTTTAGTTGCTATCGTCCTGTTCTTTGTCTAC
TACACTCATCCAGCCAGTTGTTCAGAAAACAAGGCGTTCATCAGTGTCAACATGCTCCTCTG
CGTTGGTGCTTCTGTAATGTCTATACTGCCAAAAATCCAAGAATCACAACCAAGATCTGGTT TGTTACAGTCTTCAGTAATTACAGTCTACACAATGTATTTGACATGGTCAGCTATGACCAAT GAACCAGAAACAAATTGCAACCCAAGTCTACTAAGCATAATTGGCTACAATACAACAAGCAC TGTCCCAAAGGAAGGGCAGTCAGTCCAGTGGTGGCATGCTCAAGGAATTATAGGACTAATTC TCTTTTTGTTGTGTGTATTTTATTCCAGCATCCGTACTTCAAACAATAGTCAGGTTAATAAA **AATCTCTTCCAGTTGGATTGGCATCGTGCTGTATGTTTGGACACTCGTGGCACCACTTGTTC** TTACAAATCGTGATTTTGACTGAGTGAGACTTCTAGCATGAAAGTCCCACTTTGATTATTGC TTATTTGAAAACAGTATTCCCAACTTTTGTAAAGTTGTGTATGTTTTTTGCTTCCCATGTAAC TTCTCCAGTGTTCTGGCATGAATTAGATTTTACTGCTTGTCATTTTGTTATTTTCTTACCAA AGGTTTTACCCTTGATACGGAATTTACACAGGTAGGGAGTGTTTAGTGGACAATAGTGTAGG TTATGGATGGAGGTGTCGGTACTAAATTGAATAACGAGTAAATAATCTTACTTGGGTAGAGA TGGCCTTTGCCAACAAAGTGAACTGTTTTTGGTTGTTTTAAACTCATGAAGTATGGGTTCAGT GGAAATGTTTGGAACTCTGAAGGATTTAGACAAGGTTTTGAAAAGGATAATCATGGGTTAGA AGGAAGTGTTTTGAAAGTCACTTTGAAAGTTAGTTTTTGGGCCCAGCACGGTAGCTCACCCTT GGTAATCCCAGCACTTTGGGAGCTTAAGTGGGTAGATTACTTGAGCCCAGGAATTCAGACCA TTATTCTGTGTGTAGACATTGTATTCCACAATTTTGAATGGCTGTGTTTTACCTCTAAATAA ATGAATTCAGAGAAAAAAAAAAAAA

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FIGURE 41

MGSVLGLCSMASWIPCLCGSAPCLLCRCCPSGNNSTVTRLIYALFLLVGVCVACVMLIPGME
EQLNKIPGFCENEKGVVPCNILVGYKAVYRLCFGLAMFYLLLSLLMIKVKSSSDPRAAVHNG
FWFFKFAAAIAIIIGAFFIPEGTFTTVWFYVGMAGAFCFILIQLVLLIDFAHSWNESWVEKM
EEGNSRCWYAALLSATALNYLLSLVAIVLFFVYYTHPASCSENKAFISVNMLLCVGASVMSI
LPKIQESQPRSGLLQSSVITVYTMYLTWSAMTNEPETNCNPSLLSIIGYNTTSTVPKEGQSV
QWWHAQGIIGLILFLLCVFYSSIRTSNNSQVNKLTLTSDESTLIEDGGARSDGSLEDGDDVH
RAVDNERDGVTYSYSFFHFMLFLASLYIMMTLTNWSRYEPSREMKSQWTAVWVKISSSWIGI
VLYVWTLVAPLVLTNRDFD

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FIGURE 42

GCGAGAAAGAAGCTGTCTCCATCTTGTCTGTATCCCGCTGCTTCTTGNGACGTTGTGGAGAT
GGGGAGCGTCCCTGGGGCTGTGCTCCATGGCGAGCTGGATACCATGTTTGTGTGGAAGTGCC
CCGTGTTTGCTATGCCGATGCTGTCCTAGTGGAAACAANTCCACTGTAACTAGATTGATCTA
TGCACTTTTCTTGCTTGTTGGAGTATGTGTAGCTTGTTAATGTTGATACCAGGAATGGAAG
AACAACTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAGGTGTTGTCCCTTGTAACATT
TTGGTTGGCTATAAAGCTGTATATCGTTTGTGCTTTTGGTTTGGCTATGTTCTATCTTCTT
CTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCACAATGGAT
TTTGGTTCTTTAAATTTGCTGCAGCAATTGCAATTATTATTTGGGGC

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FIGURE 43

GTTATTGTGAACTTTGTGGAGATGGGAGGTCNTGGGGCTGTGTTCCATGGCGAGCTGGATAC
CANGTTTGTGTGGAAGTGCCCCGTGTTTGNTATGCCGATGCTGTCCTAGTGGAAACAANTCC
ACTGTAATTAGATTGATNTATGCACTTTTNTTGCTTGTTGGAGTANGTGTAGCTTGTGTAAT
GTTGATACCAGGAATGGAAGAACAACTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAG
GTGTTGTCCCTTGTAACATTTTGGTTGGCTATAAAGCTGTATATNGTTTGTGCTTTGGTTTG
GCTANGTTCTATNTTCTTCTCTCTTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAG
AGCTGCAGTGCACAATGGATTTTGGTTTTTTAAATTTGCTGCAGCAATTGCAATTATTATTG
GGGC

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FIGURE 44

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FIGURE 45

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FIGURE 46

GGCAAATGTGTGTGGCTGGAGGCGAGGCGCGAGGCTTTCGGCAAAGGCAGTCGAGTGTTTGCAGACCGGGGCGAG GTCGTTTCCAGCCAAGTGGACCTGATCGATGGCCCTCCTGAATTTATCACGATATTTGATTTATTAGCGATGCC CCCTGGTTTGTGTGTTACGCACACACACGTGCACACAGGCTCTGGCTCGCTTCCCTCCTCGTTTCCAGCTCC TGGGCGAATCCCACATCTGTTTCAACTCTCCGCCGAGGGCGAGCAGGAGCGAGAGTGTGTCGAATCTGCGAGTG AAGAGGGACGAGGGAAAAGAAACAAAGCCACAGACGCAACTTGAGACTCCCGCATCCCAAAAGAAGCACCAGAT TGGAAGCTCGGCCTTCCTGTCGCACCACCGCCTGAAAGGCAGGTTTCAGAGGGACCGCAGGAACATCCGCCCCA ACATCATCCTGGTGCTGACGGACCAGGATGTGGAGCTGGGTTCCATGCAGGTGATGAACAAGACCCGGCGC ATCATGGAGCAGGGGGGGGCACTTCATCAACGCCTTCGTGACCACACCCATGTGCTGCCCCTCACGCTCCTC CATCCTCACTGGCAAGTACGTCCACAACCACAACACCTACACCAACAATGAGAACTGCTCCTCGCCCTCCTGGC AGGCACAGCACGAGAGCCGCACCTTTGCCGTGTACCTCAATAGCACTGGCTACCGGACAGCTTTCTTCGGGAAG TATCTTAATGAATACAACGCTCCTACGTGCCACCCGGCTGGAAGGAGTGGGTCGGACTCCTTAAAAACTCCCG CTTTTATAACTACACGCTGTGTCGGAACGGGGTGAAAGAGAAGCACGGCTCCGACTACTCCAAGGATTACCTCA ${\tt CAGACCTCATCACCAATGACAGCGTGAGCTTCTTCCGCACGTCCAAGAAGATGTACCCGCACAGGCCAGTCCTC}$ ATGGTCATCAGCCATGCAGCCCCCACGGCCCTGAGGATTCAGCCCCACAATATTCACGCCTCTTCCCAAACGC ATCTCAGCACATCACGCCGAGCTACAACTACGCGCCCAACCCGGACAAACACTGGATCATGCGCTACACGGGGC CCATGAAGCCCATCCACATGGAATTCACCAACATGCTCCAGCGGAAGCGCTTGCAGACCCTCATGTCGGTGGAC GACTCCATGGAGACGATTTACAACATGCTGGTTGAGACGGGCGAGCTGGACAACACGTACATCGTATACACCGC CGACCACGGTTACCACATCGGCCAGTTTGGCCTGGTGAAAGGGAAATCCATGCCATATGAGTTTGACATCAGGG TCCCGTTCTACGTGAGGGGCCCCAACGTGGAAGCCGGCTGTCTGAATCCCCACATCGTCCTCAACATTGACCTG GGACACGGAGCGGCCGGTGAATCGGTTTCACTTGAAAAAGAAGATGAGGGTCTGGCGGGACTCCTTCTTGGTGG AGAGAGCCAAGCTGCTACACAAGAGAGACAATGACAAGGTGGACGCCCAGGAGGAGAACTTTCTGCCCAAGTAC CAGCGTGTGAAGGACCTGTGTCAGCGTGCTGAGTACCAGACGGCGTGTGAGCAGCTGGGACAGAAGTGGCAGTG TGTGGAGGACGCCACGGGGAAGCTGAAGCTGCATAAGTGCAAGGGCCCCATGCGGCTGGGCGGCAGCAGAGCCC ${\tt TCTCCAACCTCGTGCCCAAGTACTACGGGCAGGGCAGCGAGGCCTGCACCTGTGACAGCGGGGGACTACAAGCTC}$ AGCCTGGCCGGACGCCGGAAAAAACTCTTCAAGAAGAAGTACAAGGCCAGCTATGTCCGCAGTCGCTCCATCCG CTCAGTGGCCATCGAGGTGGACGGCAGGGTGTACCACGTAGGCCTGGGTGATGCCGCCCAGCCCCGAAACCTCA CCAAGCGGCACTGGCCAGGGCCCCTGAGGACCAAGATGACAAGGATGGTGGGGACTTCAGTGGCACTGGAGGC CTTCCCGACTACTCAGCCGCCAACCCCATTAAAGTGACACATCGGTGCTACATCCTAGAGAACGACACAGTCCA GTGTGACCTGGACCTGTACAAGTCCCTGCAGGCCTGGAAAGACCACAAGCTGCACATCGACCACGAGATTGAAA CCCTGCAGAACAAATTAAGAACCTGAGGGAAGTCCGAGGTCACCTGAAGAAAAAGCGGCCAGAAGAATGTGAC TGTCACAAAATCAGCTACCACCCAGCACAAAGGCCGCCTCAAGCACAGAGGCTCCAGTCTGCATCCTTTCAG GAAGGGCCTGCAAGAGAAGGACAAGGTGTGGCTGTTGCGGGAGCAGAAGCGCAAGAAGAAACTCCGCAAGCTGC TCAAGCGCCTGCAGAACAACGACACGTGCAGCATGCCAGGCCTCACGTGCTTCACCCACGACAACCAGCACTGG CAGACGGCGCCTTTCTGGACACTGGGGCCTTTCTGTGCCTGCACCAGCGCCAACAATAACACGTACTGGTGCAT GAGGACCATCAATGAGACTCACAATTTCCTCTTCTGTGAATTTGCAACTGGCTTCCTAGAGTACTTTGATCTCA ACACAGACCCCTACCAGCTGATGAATGCAGTGAACACACTGGACAGGGATGTCCTCAACCAGCTACACGTACAG AAGCTATGAGCAATACAGGCAGTTTCAGCGTCGAAAGTGGCCAGAAATGAAGAGACCTTCTTCCAAATCACTGG GACAACTGTGGGAAGGCTGGGAAGGT<u>TAA</u>GAAACAACAGAGGTGGACCTCCAAAAACATAGAGGCATCACCTGA CTGCACAGGCAATGAAAAACCATGTGGGTGATTTCCAGCAGACCTGTGCTATTGGCCAGGAGGCCTGAGAAAGC AAGCACGCACTCTCAGTCAACATGACAGATTCTGGAGGATAACCAGCAGGAGCAGAGATAACTTCAGGAAGTCC ATTTTTGCCCCTGCTTTTGCTTTGGATTATACCTCACCAGCTGCACAAAATGCATTTTTTCGTATCAAAAAGTC TCCCAAGGGCGAAAGTCATTGGAATTTTTAAATCATAGGGGAAAAGCAGTCCTGTTCTAAATCCTCTTATTCTT TTGGTTTGTCACAAAGAAGGAACTAAGAAGCAGGACAGAGGCAACGTGGAGAGGCTGAAAACAGTGCAGAGACG TTTGACAATGAGTCAGTAGCACAAAAGAGATGACATTTACCTAGCACTATAAACCCTGGTTGCCTCTGAAGAAA CTGCCTTCATTGTATATATGTGACTATTTACATGTAATCAACATGGGAACTTTTAGGGGGAACCTAATAAGAAAT CCCAATTTTCAGGAGTGGTGTGTCAATAAACGCTCTGTGGCCAGTGTAAAAGAAAAA

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FIGURE 47

MGPPSLVLCLLSATVFSLLGGSSAFLSHHRLKGRFQRDRRNIRPNIILVLTDDQDVELGSMQ
VMNKTRIMEQGGAHFINAFVTTPMCCPSRSSILTGKYVHNHNTYTNNENCSSPSWQAQHES
RTFAVYLNSTGYRTAFFGKYLNEYNGSYVPPGWKEWVGLLKNSRFYNYTLCRNGVKEKHGSD
YSKDYLTDLITNDSVSFFRTSKKMYPHRPVLMVISHAAPHGPEDSAPQYSRLFPNASQHITP
SYNYAPNPDKHWIMRYTGPMKPIHMEFTNMLQRKRLQTLMSVDDSMETIYNMLVETGELDNT
YIVYTADHGYHIGQFGLVKGKSMPYEFDIRVPFYVRGPNVEAGCLNPHIVLNIDLAPTILDI
AGLDIPADMDGKSILKLLDTERPVNRFHLKKKMRVWRDSFLVERGKLLHKRDNDKVDAQEEN
FLPKYQRVKDLCQRAEYQTACEQLGQKWQCVEDATGKLKLHKCKGPMRLGGSRALSNLVPKY
YGQGSEACTCDSGDYKLSLAGRRKKLFKKKYKASYVRSRSIRSVAIEVDGRVYHVGLGDAAQ
PRNLTKRHWPGAPEDQDDKDGGDFSGTGGLPDYSAANPIKVTHRCYILENDTVQCDLDLYKS
LQAWKDHKLHIDHEIETLQNKIKNLREVRGHLKKKRPEECDCHKISYHTQHKGRLKHRGSSL
HPFRKGLQEKDKVWLLREQKRKKKLRKLLKRLQNNDTCSMPGLTCFTHDNQHWQTAPFWTLG
PFCACTSANNNTYWCMRTINETHNFLFCEFATGFLEYFDLNTDPYQLMNAVNTLDRDVLNQL
HVQLMELRSCKGYKQCNPRTRNMDLDGGSYEQYRQFQRRKWPEMKRPSSKSLGQLWEGWEG

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FIGURE 48

AACAAAGTTCAGTGACTGAGAGGGCTGAGCGGAGGCTGCTGAAGGGGGAAAAGGAGTGAGGA GCTGCTGGGCAGAGAGGGACTGTCCGGCTCCCAGATGCTGGGCCTCCTGGGGAGCACAGCCC TCGTGGGATGATCACAGGTGCTGCTGTGGCGGTCCTGCTGCTGCTGCTGCTGCCACC TGCCTTTTCCACGGACGCAGGACTGTGACGTGGAGAGCGAACCGTACAGCTGCAGGGGGAAA CCGAGTCCGCCGGGCCCAGCCTTGGCCCTTCCGGCGGGGGCCACCTGGGAATCTTTCACC ATCACCGTCATCCTGGCCACGTATCTCATGTGCCGAATGTGGGCCTCCACCACCACCACCAC CCCCGCCACACCCCTCACCACCACCACCACCACCCCCACCGCCACCATCCCCGCCA CGCTCGCTGAGGCTGCTGTCGCCGGTGCCTGTGGACAGCAGCTGCCCCTGCCCTCCCATCTG TTCCCAGGACAAGTGGACCCCATGTTTCCATGTGGAAGGATGCATCTCTGGGGTGAACGAGG GGAACAATAGACTGGGGCTTGCTCCAGCTGCATTTGCATGGCATGCCCCAGTGTACTATGGC AGCAGAGAATGGAGGAACACTGGGTCTGCAGTGCTGAAGGGTTTGGGGAGTGGAGAGCAAGG GTGCTCTTTCGGGGCTGGACAGCCCGTCTTGTGACAGTGACTCCCAGTGAGCCCCAGAAATG ACAAGCGTGTCTTGGCAGAGCCAGCACAAGTGGATGTGAAGTGCCCGTCTTGACCTCCTC ATCAGGCTGCTGCAGGCCTCTGGCGGCCAGGGCACTGGGAGAGGCCCTGAGAATGTCCTTTT GGTTTGGAGAAGGCAGTGTGAGGCTGCACAGTCAATTCATCGGTGCCTTAGTCCAAGAAAAT

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FIGURE 49

MLGLLGSTALVGWITGAAVAVLLLLLLLATCLFHGRQDCDVERNRTAAGGNRVRRAQPWPFR RRGHLGIFHHHRHPGHVSHVPNVGLHHHHHPRHTPHHLHHHHHPHRHHPRHAR

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FIGURE 50

GGCGGCTGCTGAGCTGCCTTGAGGTGCAGTGTTGGGGATCCAGAGCCATGTCGGACCTGCTA CTACTGGGCCTGATTGGGGGCCTGACTCTTTACTGCTGCTGACGCTGCTGGCCTTTGCCGG GTACTCAGGGCTACTGGCTGGGGTGGAAGTGAGTGCTGGGTCACCCCCCATCCGCAACGTCA CTGTGGCCTACAAGTTCCACATGGGGCTCTATGGTGAGACTGGGCGGCTTTTCACTGAGAGC TGCAGCATCTCTCCCAAGCTCCGCTCCATCGCTGTCTACTATGACAACCCCCACATGGTGCC CCCTGATAAGTGCCGATGTGCCGTGGGCAGCATCCTGAGTGAAGGTGAGGAATCGCCCTCCC CTGAGCTCATCGACCTCTACCAGAAATTTGGCTTCAAGGTGTTCTCCTTCCCGGCACCCAGC TGTCCATCCTGCCTTGGACACCTACATCAAGGAGCGGAAGCTGTGTGCCTATCCTCGGCTGG AGATCTACCAGGAAGACCAGATCCATTTCATGTGCCCACTGGCACGGCAGGGAGACTTCTAT GTGCCTGAGATGAAGGAGACAGAGTGGAAATGGCGGGGGCTTGTGGAGGCCATTGACACCCA GGTGGATGGCACAGGAGCTGACACAATGAGTGACACGAGTTCTGTAAGCTTGGAAGTGAGCC CTGGCAGCCGGGAGACTTCAGCTGCCACACTGTCACCTGGGGCGAGCAGCCGTGGCTGGGAT GACGGTGACACCCGCAGCGAGCACAGCTACAGCGAGTCAGGTGCCAGCGGCTCCTCTTTTGA GGAGCTGGACTTGGAGGGCCGAGGGGCCCTTAGGGGAGTCACGGCTGGACCCTGGGACTGAGC CCCTGGGGACTACCAAGTGGCTCTGGGAGCCCACTGCCCCTGAGAAGGGCAAGGAG<u>TAA</u>CCC ATGGCCTGCACCCTCCTGCAGTGCAGTTGCTGAGGAACTGAGCAGACTCTCCAGCAGACTCT CCAGCCCTCTTCCTCCTCTGGGGGGGGGGGGTTCCTGAGGGACCTGACTTCCCCTGC TCCAGGCCTCTTGCTAAGCCTTCTCCTCACTGCCCTTTAGGCTCCCAGGGCCAGAGGAGCCA GGGACTATTTTCTGCACCAGCCCCCAGGGCTGCCGCCCCTGTTGTGTCTTTTTTTCAGACTC ACAGTGGAGCTTCCAGGACCCAGAATAAAGCCAATGATTTACTTGTTTCACCTGGAAAAAAA AAAAAAAAA

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FIGURE 51

MSDLLLGLIGGLTLLLLTLLAFAGYSGLLAGVEVSAGSPPIRNVTVAYKFHMGLYGETGR LFTESCSISPKLRSIAVYYDNPHMVPPDKCRCAVGSILSEGEESPSPELIDLYQKFGFKVFS FPAPSHVVTATFPYTTILSIWLATRRVHPALDTYIKERKLCAYPRLEIYQEDQIHFMCPLAR QGDFYVPEMKETEWKWRGLVEAIDTQVDGTGADTMSDTSSVSLEVSPGSRETSAATLSPGAS SRGWDDGDTRSEHSYSESGASGSSFEELDLEGEGPLGESRLDPGTEPLGTTKWLWEPTAPEK GKE

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FIGURE 52

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FIGURE 53

MTLRPSLLPLHLLLLLLSAAVCRAEAGLETESPVRTLQVETLVEPPEPCAEPAAFGDTLHI HYTGSLVDGRIIDTSLTRDPLVIELGQKQVIPGLEQSLLDMCVGEKRRAIIPSHLAYGKRGF PPSVPADAVVQYDVELIALIRANYWLKLVKGILPLVGMAMVPALLGLIGYHLYRKANRPKVS KKKLKEEKRNKSKKK

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FIGURE 54

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FIGURE 55

CCGAAAGTCCCGTCCGGACCCTCCAAGTGGAGACCCTGGTGGAGCCCCCAGAACCATGTGCC
GAGCCCGCTGCTTTTGGAGACACGCTTCACATACACTACACGGGAAGCTTGGTAGATGGACG
TATTATTGACACCTCCCTGACCAGAGACCCTCTGGTTATAGAACTTGGCCAAAAGCAGGTGA
TTCCAGGTCTGGAGCAGAGTCTTCTCGACATGTGTGTGGGAGAAGCGAAGGGCAATCATT
CCTTCTCACTTGGCCTATGGAAAACGGGGATTTCCACCATCTGTCCCAGCGGATGCAGTGGT
GCAGTATGACGTGGAGCTGATTGCACTAATCCGAGCCAACTACTGGCTAAAGCTGGTGAAGG
GCATTTTGCCTCTGGTAGGGATGGCCATGGTGCCAGCCCTCCTGGGCCTCATTGGGTATCAC
CTATACAGAAAGGCCAATAGACCCAAAGTCTCCAAAAAGAAGCTCAAGGAAGAAACGAAA

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FIGURE 56

CTGCTGCATCCGGGTGTCTGGAGGCTGTGGCCGTTTTGTTTTCTTGGCTAAAATCGGGGGAG TGAGGCGGGCGGCGCGCGACACCGGGCTCCGGAACCACTGCACGACGGGGCTGGACTG ACCTGAAAAAAATGTCTGGATTTCTAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGG GAAAAGCGCAATACTATTGCTTCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGGTGGAT TATCATAGATGCAGCTGTTATTTATCCCACCATGAAAGATTTCAACCACTCATACCATGCCT GTGGTGTTATAGCAACCATAGCCTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGA GGTGATAGTTACAGTGAAGGTTGTCTGGGTCAAACAGGTGCTCGCATTTGGCTTTTCGTTGG TTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTGGAGGTTATGTTG CTAAAGAAAAAGACATAGTATACCCTGGAATTGCTGTATTTTTCCAGAATGCCTTCATCTTT TTTGGAGGGCTGGTTTTTAAGTTTGGCCGCACTGAAGACTTATGGCAG**TGA**ACACATCTGAT TTCCCACAGCACAACAGCCCTGCATGGGTTTGTTTGTTTTTTTACTGCTCACTCCCAACCTT TTGTAATGCCATTTTCTAAACTTATTTCTGAGTGTAGTCTCAGCTTAAAGTTGTGTAATACT AAAATCACGAGAACACCTAAACAACAACCAAAAATCTATTGTGGTATGCACTTGATTAACTT ATAAAATGTTAGAGGAAACTTTCACATGAATAATTTTTGTCAAATTTTATCATGGTATAATT TGTAAAAATAAAAGAAATTACAAAAGAAATTATGGATTTGTCAATGTAAGTATTTGTCATA TCTGAGGTCCAAAACCACAATGAAAGTGCTCTGAAGATTTAATGTGTTTATTCAAATGTGGT CTCTTCTGTGTCAAATGTTAAATGAAATATAAACATTTTTTAGTTTTTAAAATATTCCGTGG TCAAAATTCTTCCTCACTATAATTGGTATTTACTTTTACCAAAAATTCTGTGAACATGTAAT GTAACTGGCTTTTGAGGGTCTCCCAAGGGGTGAGTGGACGTGTTGGAAGAGAAGAAGCACCAT GGTCCAGCCACCAGGCTCCCTGTGTCCCTTCCATGGGAAGGTCTTCCGCTGTGCCTCTCATT CCAAGGCAGGAAGATGTGACTCAGCCATGACACGTGGTTCTGGTGGGATGCACAGTCACTC CACATCCACCACTG

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FIGURE 57

MSGFLEGLRCSECIDWGEKRNTIASIAAGVLFFTGWWIIIDAAVIYPTMKDFNHSYHACGVI ATIAFLMINAVSNGQVRGDSYSEGCLGQTGARIWLFVGFMLAFGSLIASMWILFGGYVAKEK DIVYPGIAVFFQNAFIFFGGLVFKFGRTEDLWQ

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FIGURE 58

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FIGURE 59

TGGACGACCTGAAAAAAATGTTTGGATTTNTAGAGGGNTTGAGATGTTCAGAATGCATGAC
TGGGGGAAAAGCGCAAATACTATTGCTTCCATTGCTGCTGGTGTANTATTTTTTACAGGCTG
GTGGATTATCATAGATGCAGNTGTTATTTATCCCACCATGAAAGATTTCAACCANTCATACC
ATGCCTGTGGTGTTATAGCAACCATAGCCTTCNTAATGATTAATGCAGTATCGAATGGACAA
GTCCGAGGTGATAGTTACAGTGAAGGTTGTTTGGGTCAAACAGGTGCTCGCATTTGGCTTTT
CGTTGGTTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTGGAGGTT
ATGTTGCTAAAGAAAAAGACATAGTATACCCTGGAATTGNTGTATTTTTCCAGAATGCCTTC
ATCTTTTTTGGAGGGCTGGTTTTTAAGTTTGGCCGCACTGAAGANTTATGGCAGTG

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FIGURE 60

GGACACCGGGTTCCGGACCAATGCANGACGGGGTGGANTGACCTGAAAAAAATGTTTGGATT
TTTAGAGGGCTTGAGATGNTCAGAATGCATTGACTGGGGGAAAAGCGCAATANTATTGCTTT
CCATTGCTGCTGGTGTACTATTTTTTACAGGGTGGTGGATTATCATAGATGCAGCTGTTATT
TATCCCACCATGAAAGATTTNAACCACTCATACCATGCCTGTGGTGTTATAGCAACCATAGC
CTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTT
GTTTGGGTCAAACAGGTGNTCGCATTTGGCTTTTCGTTGGTTTCATGTTGGCCTTTGGATTT
CTGATTGNATTCTATGCGGATTCTTCTTGGAGGTTATGTTGCTAAAGAAAAAAGACATAGTAT
ACCCTGGAATTNCTNTATTTTTCCAGAATGCC

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FIGURE 61

TAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGGGAAAAGCGCAATANTATTGCTTCC
ATTGNTGNTGGTGTANTATTTTTTTACAGGCTGGTGGATTATNATAGATGCAGCTGTTATTT
ATCCCACCATGAAAGATTTNAACCANTCATACCATGCCTGTGGTGTTATAGCAACCATAGCC
TTCCTAATGATTAATGCAGTATNGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTTG
TTTGGGTCAAACAGGTGNTNGCATTTGGCTTTTNGTTGGTTTCATGTTGGCCTTTTGGATCTN
TGATTGCATTTATGTGGATTNTTTTTGGAGGTTATGTTGCTAAAGNAAAAGACATAGTATAC
CCTGT

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FIGURE 62

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FIGURE 63

CGACGCCGGCGTGATCTGGCTTCCGCTGGTGCTCCTGGCTGTGCTGCTGCTGCCGTCC
TCTGCAAAGTTTACTTGGGACTATTCTCTGGCAGCTCCCCGAATCCTTTCTCCGAAGATGTC
AAACGGCCCCCAGCGCCCCTGGTAACTGACAAGGAGGCCAGGAAGAAGGTTCTCAAACAAGC
TTTTTCAGCCAACCAAGTGCCGGAGAAGCTGGATGTGTGGTGGTAATTGGCAGTGGCTTTGGGG TTTTTCAGCCAACCAAGTGCCGGAGAAGCTGGATGTGGTGGTAATTGGCAGTGGCTTTGGGG GCCTGGCTGCAGCTGCAATTCTAGCTAAAGCTGGCAAGCGAGTCCTGGTGCTGGAACAACAT ACCAAGGCAGGGGGCTGCTGTCATACCTTTGGAAAGAATGGCCTTGAATTTGACACAGGAAT CCATTACATTGGGCGTATGGAAGAGGGCAGCATTGGCCGTTTTATCTTGGACCAGATCACTG AAGGGCAGCTGGACTGGGCTCCCCTGTCCTCTCTTTTTGACATCATCATTCAGGCCCTCAAGGACCC AATGGCCGAAAGGAGTACCCCATGTACAGTGGAGAAAAGCCTACATTCAGGGCCTCAATGGA GAAGTTTCCACAGGAGGAAGCTATCATTGACAAGTATATAAAGCTGGTTAAGGTGGTATCCA GTGGAGCCCCTCATGCCATCCTGTTGAAATTCCTCCCATTGCCCGTGGTTCAGCTCCTCGAC AGGTGTGGGCTGCTGACTCGTTTCTCCCATTCCTTCAAGCATCCACCCAGAGCCTGGCTGA GGTCCTGCAGCAGCTGGGGGCCTCCTCTGAGCTCCAGGCAGTACTCAGCTACATCTTCCCCA TGGACTGGTAAGATGAATACTTTGCTGGGCTGAAGCAGGCTGCAGGGCATTCCAGCCAAGGG CACAGCAGGGGACAGTGCAGGGAGGTGTGGGGTAAGGGAAGTCACATCAGAAAAGGGA AAGCCACGGAATGTGTGAAGCCCAGAAATGGCATTTGCAGTTAATTAGCACATGTGAGGG TTAGACAGGTAGGTGAATGCAAGCTCAAGGTTTGGAAAAATGACTTTTCAGTTATGTCTTTTG GTATCAGACATACGAAAGGTCTCTTTGTAGTTCGTGTTAATGTAACATTAATAAATTTATTG ATTCCATTGCTTTAAAAAAAAAAAAAAAA

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FIGURE 64

MWLPLVLLLAVLLLAVLCKVYLGLFSGSSPNPFSEDVKRPPAPLVTDKEARKKVLKQAFSAN QVPEKLDVVVIGSGFGGLAAAAILAKAGKRVLVLEQHTKAGGCCHTFGKNGLEFDTGIHYIG RMEEGSIGRFILDQITEGQLDWAPLSSPFDIMVLEGPNGRKEYPMYSGEKAYIQGLKEKFPQ EEAIIDKYIKLVKVVSSGAPHAILLKFLPLPVVQLLDRCGLLTRFSPFLQASTQSLAEVLQQ LGASSELQAVLSYIFPTYGVTPNHSAFSMHALLVNHYMKGGFYPRGGSSEIAFHTIPVIQRA GGAVLTKATVQSVLLDSAGKACGVSVKKGHELVNIYCPIVVSNAGLFNTYEHLLPGNARCLP GVKQQLGTVRPGLGMTSVFICLRGTKEDLHLPSTNYYVYYDTDMDQAMERYVSMPREEAAEH IPLLFFAFPSAKDPTWEDRFPGRSTMIMLIPTAYEWFEEWQAELKGKRGSDYETFKNSFVEA SMSVVLKLFPQLEGKVESVTAGSPLTNQFYLAAPRGACYGADHDLGRLHPCVMASLRAQSPI PNLYLTGQDIFTCGLVGALQGALLCSSAILKRNLYSDLKNLDSRIRAQKKKN

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FIGURE 65

GCAGCGGCGAGGCGGCGGTGGTGGCTGAGTCCGTGGTGGCAGAGGCGAAGGCGACAGCTCTA GGGGTTGGCACCGGCCCCGAGAGGAGGAGGATGCGGGTCCGGATAGGGCTGACGCTGCTGTG TGCGGTGCTGAGCTTGGCCTCGGCGTCCTCGGATGAAGAAGGCAGCCAGGATGAATCCT GTAGTTGCTGGTCAAATATTTCTTGATTCAGAAGAATCTGAATTAGAATCCTCTATTCAAGA AGAGGAAGACAGCCTCAAGAGCCAAGAGGGGGAAAGTGTCACAGAAGATATCAGCTTTCTAG ACCGCCATTGAAGGCACAGCACATGGGGAGCCCTGCCACTTCCCTTTTCTTTTCCTAGATAA GGAGTATGATGAATGTACATCAGATGGGAGGGAAGATGGCAGACTGTGGTGTGCTACAACCT ATGACTACAAAGCAGATGAAAAGTGGGGCTTTTGTGAAACTGAAGAAGAGGCTGCTAAGAGA CGGCAGATGCAGGAAGCAGAAATGATGTATCAAACTGGAATGAAAATCCTTAATGGAAGCAA CCAAAGCCCTGGAGAGAGTGTCATATGCTCTTTTATTTGGTGATTACTTGCCACAGAATATC CAGGCAGCGAGAGATGTTTGAGAAGCTGACTGAGGAAGGCTCTCCCAAGGGACAGACTGC TCTTGGCTTTCTGTATGCCTCTGGACTTGGTGTTAATTCAAGTCAGGCAAAGGCTCTTGTAT ATTATACATTTGGAGCTCTTGGGGGCAATCTAATAGCCCACATGGTTTTGGTAAGTAGACTT **TAG**TGGAAGGCTAATAATATTAACATCAGAAGAATTTGTGGTTTATAGCGGCCACAACTTTT ATTCTTGTTAATGGATATAACACATGGAATCTACATGTAAATGAAAGTTGGTGGAGTCCACA ATTTTTCTTTAAAATGATTAGTTTGGCTGATTGCCCCTAAAAAGAGAGATCTGATAAATGGC TCTTTTTAAATTTTCTCTGAGTTGGAATTGTCAGAATCATTTTTTACATTAGATTATCATAA TTTTAAAAATTTTTCTTTAGTTTTTCAAAATTTTGTAAATGGTGGCTATAGAAAAACAACAT GAAATATTATACAATATTTTGCAACAATGCCCTAAGAATTGTTAAAATTCATGGAGTTATTT GTGCAGAATGACTCCAGAGAGCTCTACTTTCTGTTTTTTACTTTTCATGATTGGCTGTCTTC CCATTTATTCTGGTCATTTATTGCTAGTGACACTGTGCCTGCTTCCAGTAGTCTCATTTTCC CTATTTTGCTAATTTGTTACTTTTCTTTGCTAATTTGGAAGATTAACTCATTTTTAATAAA AAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 66

MRVRIGLTLLLCAVLLSLASASSDEEGSQDESLDSKTTLTSDESVKDHTTAGRVVAGQIFLD SEESELESSIQEEEDSLKSQEGESVTEDISFLESPNPENKDYEEPKKVRKPALTAIEGTAHG EPCHFPFLFLDKEYDECTSDGREDGRLWCATTYDYKADEKWGFCETEEEAAKRRQMQEAEMM YQTGMKILNGSNKKSQKREAYRYLQKAASMNHTKALERVSYALLFGDYLPQNIQAAREMFEK LTEEGSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLIAHMVLVSRL

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FIGURE 67

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FIGURE 68

MACRCLSFLLMGTFLSVSQTVLAQLDALLVFPGQVAQLSCTLSPQHVTIRDYGVSWYQQRAG SAPRYLLYYRSEEDHHRPADIPDRFSAAKDEAHNACVLTISPVQPEDDADYYCSVGYGFSP

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FIGURE 69

GGGGGACCCGCCGCCGCTGACCATGTGGACCAAGGATGGCCGCACCATCCACAGCGGCTGGA GCCGCTTCCGCGTGCTGCCGCAGGGGCTGAAGGTGAAGCAGGTGGAGCGGAGGATGCCGGCGTGTACGTGTGCAAGGCCACCAACGGCTTCGGCAGCCTGAGCGTCAACTACACCCTCGTCGT GCGGACCCGTTCCAAGCCCGTGCTCACAGGCACGCACCCCGTGAACACGACGGTGGACTTCG GGGGGACCACGTCCTTCCAGTGCAAGGTGCGCAGCGACGTGAAGCCGGTGATCCAGTGGCTG AAGCGCGTGGAGTACGGCGCCGAGGGCCCACAACTCCACCATCGATGTGGGCGGCCAGAA GTTTGTGGTGCTGCCCACGGGTGACGTGTGGTCGCGCCCGACGGCTCCTACCTCAATAAGC ACACTCACACGTGGAGGGCAAGGTCCACCAGCACATCCACTATCAGTGCTAGACGGCACCGT ATCTGCAGTGGGCACGGGGGGCCGGCCAGACAGGCAGACTGGGAGGATGGAGGACGGAGCT GCAGACGAAGGCAGGGGACCCATGGCGAGGAGGAATGGCCAGCACCCCAGGCAGTCTGTGTG TGAGGCATAGCCCCTGGACACACACACACACACACACACTACCTGGATGCATGTATGCAC ACACATGCGCGCACACGTGCTCCCTGAAGGCACACGTACGCACACGCACATGCACAGATATG CATCCCCCCTCTCCCCTGCCCTTGCCGCTATTTTTTGCCACCTGCCTTGGGTGCCCAGG
AGTCCCCTACTGCTGTGGGGTTGGGGGCACAGCAGCCCCAAGCCTGAGAGGCTGGAG
CCCATGGCTAGTGGCTCATCCCCAGTGCATTCTCCCCCTGACACAGAGAAGGGGCCTTGGTA
TTTATATTTAAGAAATGAAGATAATATTAATAATGATGGAAGGAAGACTGGGTTGCAGGGAC TGTGGTCTCCTGGGGCCCGGGACCCGCCTGGTCTTTCAGCCATGCTGATGACCACACCCCGTCCAGGCCAGACACCACCCCCACTGTCGTGGTGGCCCCAGATCTCTGTAATTTTATTTTGTTAAACACAAAA

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FIGURE 70

MTPSPLLLLLPPLLLGAFPPAAAARGPPKMADKVVPRQVARLGRTVRLQCPVEGDPPPLTM
WTKDGRTIHSGWSRFRVLPQGLKVKQVEREDAGVYVCKATNGFGSLSVNYTLVVLDDISPGK
ESLGPDSSSGGQEDPASQQWARPRFTQPSKMRRRVIARPVGSSVRLKCVASGHPRPDITWMK
DDQALTRPEAAEPRKKKWTLSLKNLRPEDSGKYTCRVSNRAGAINATYKVDVIQRTRSKPVL
TGTHPVNTTVDFGGTTSFQCKVRSDVKPVIQWLKRVEYGAEGRHNSTIDVGGQKFVVLPTGD
VWSRPDGSYLNKLLITRARQDDAGMYICLGANTMGYSFRSAFLTVLPDPKPPGPPVASSSSA
TSLPWPVVIGIPAGAVFILGTLLLWLCQAQKKPCTPAPAPPLPGHRPPGTARDRSGDKDLPS
LAALSAGPGVGLCEEHGSPAAPQHLLGPGPVAGPKLYPKLYTDIHTHTHTHSHTHSHVEGKV
HQHIHYQC

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FIGURE 71

CCCAGCTGAGGAGCCCTGCTCAAGACACGGTCACTGGATCTGAGAAACTTCCCAGGGGACCGCATTCCAGAGTC CCAGTGTAGCCCAGGGCAGATGTCAATAAATGCATACTCTGTATTTCGAAAAAA

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FIGURE 72

MVGTKAWVFSFLVLEVTSVLGRQTMLTQSVRRVQPGKKNPSIFAKPADTLESPGEWTTWFNI DYPGGKGDYERLDAIRFYYGDRVCARPLRLEARTTDWTPAGSTGOVVHGSPREGFWCLNREQ RPGONCSNYTVRFLCPPGSLRRDTERIWSPWSPWSKCSAACGOTGVOTRTRICLAEMVSLCS EASEEGOHCMGQDCTACDLTCPMGQVNADCDACMCODFMLHGAVSLPGGAPASGAAIYLLTK TPKLLTOTDSDGRFRIPGLCPDGKSILKITKVKFAPIVLTMPKTSLKAATIKAEFVRAETPY MVMNPETKARRAGQSVSLCCKATGKPRPDKYFWYHNDTLLDPSLYKHESKLVLRKLQQHQAG EYFCKAQSDAGAVKSKVAQLIVTASDETPCNPVPESYLIRLPHDCFQNATNSFYYDVGRCPV KTCAGOODNGIRCRDAVONCCGISKTEEREIOCSGYTLPTKVAKECSCORCTETRSIVRGRV SAADNGEPMRFGHVYMGNSRVSMTGYKGTFTLHVPQDTERLVLTFVDRLQKFVNTTKVLPFN KKGSAVFHEIKMLRRKEPITLEAMETNIIPLGEVVGEDPMAELEIPSRSFYRQNGEPYIGKV KASVTFLDPRNISTATAAQTDLNFINDEGDTFPLRTYGMFSVDFRDEVTSEPLNAGKVKVHL DSTQVKMPEHISTVKLWSLNPDTGLWEEEGDFKFENQRRNKREDRTFLVGNLEIRERRLFNL DVPESRRCFVKVRAYRSERFLPSEQIQGVVISVINLEPRTGFLSNPRAWGRFDSVITGPNGA CVPAFCDDQSPDAYSAYVLASLAGEELQAVESSPKFNPNAIGVPQPYLNKLNYRRTDHEDPR VKKTAFQISMAKPRPNSAEESNGPIYAFENLRACEEAPPSAAHFRFYQIEGDRYDYNTVPFN EDDPMSWTEDYLAWWPKPMEFRACYIKVKIVGPLEVNVRSRNMGGTHRRTVGKLYGIRDVRS TRDRDQPNVSAACLEFKCSGMLYDODRVDRTLVKVIPOGSCRRASVNPMLHEYLVNHLPLAV NNDTSEYTMLAPLDPLGHNYGIYTVTDQDPRTAKEIALGRCFDGTSDGSSRIMKSNVGVALT FNCVERQVGRQSAFQYLQSTPAQSPAAGTVQGRVPSRRQQRASRGGQRQGGVVASLRFPRVA QQPLIN

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FIGURE 73

CTGCAAGTTGTTAACGCCTAACACACAAGTATGTTAGGCTTCCACCAAAGTCCTCAATATACCTGAATACGCAC AAGCTCTGCTTTAGTTTCCAAGAAGATTACAAAGAATTTAGAGATCTCTGTCAAGATCCCTGTCGATTCATG CCCTTTGGGTTACGGTGTCCTCAGTGATGCAGCCCTACCCTTTGGTTTGGGGACATTATGATTTGTGTAAGACT CAGATTTACACGGAAGAAGGGAAAGTTTGGGATTACATGGCCTGCCAGCCGGAATCCACGGACATGACAAAATA TCTGAAAGTGAAACTCGATCCTCCGGATATTACCTGTGGAGACCCTCCTGAGACGTTCTGTGCAATGGGCAATC CCTACATGTGCAATAATGAGTGTGATGCGAGTACCCCTGAGCTGGCACACCCCCCTGAGCTGATGTTTGATTTT GAAGGAAGACATCCCTCCACATTTTGGCAGTCTGCCACTTGGAAGGAGTATCCCAAGCCTCTCCAGGTTAACAT CACTCTGTCTTGGAGCAAAACCATTGAGCTAACAGACAACATAGTTATTACCTTTGAATCTGGGCGTCCAGACC AAATGATCCTGGAGAAGTCTCTCGATTATGGACGAACATGGCAGCCCTATCAGTATTATGCCACAGACTGCTTA GATGCTTTTCACATGGATCCTAAATCCGTGAAGGATTTATCACAGCATACGGTCTTAGAAATCATTTGCACAGA AGAGTACTCAACAGGGTATACAACAAATAGCAAAATAATCCACTTTGAAATCAAAGACAGGTTCGCGCTTTTTG CTGGACCTCGCCTACGCAATATGGCTTCCCTCTACGGACAGCTGGATACAACCAAGAAACTCAGAGATTTCTTT ACAGTCACAGACCTGAGGATAAGGCTGTTAAGACCAGCCGTTGGGGAAATATTTGTAGATGAGCTACACTTGGC ACGCTACTTTTACGCGATCTCAGACATAAAGGTGCGAGGAAGGTGCAAGTGTAATCTCCATGCCACTGTATGTG TGTATGACAACAGCAAATTGACATGCGAATGTGAGCACAACACTACAGGTCCAGACTGTGGGAAATGCAAGAAG AATTATCAGGGCCGACCTTGGAGTCCAGGCTCCTATCTCCCCATCCCCAAAGGCACTGCAAATACCTGTATCCC CAGTATTTCCAGTATTGGTACGAATGTCTGCGACAACGAGCTCCTGCACTGCCAGAACGGAGGGACGTGCCACA ACAACGTGCGCTGCCTGCCCGGCCGCATACACGGGCATCCTCTGCGAGAAGCTGCGGTGCGAGGAGGCTGGC AGCTGCGGCTCCGACTCTGGCCAGGGCGCCCCCGCACGGCACCCCAGCGCTGCTGCTGACCACGCTGCT ${\tt GGGAACCGCCAGCCCCTGGTGTTC} \underline{{\tt TAG}}{\tt GTGTCACCTCCAGCCACACCGGACGGCCTGTGCCGTGGGGAAGCA}$ CTAAGAAGGCCTAACTGAACTAAGCCATATTTATCACCCGTGGACAGCACATCCGAGTCAAGACTGTTAATTTC TGACTCCAGAGGAGTTGGCAGCTGTTGATATTATCACTGCAAATCACATTGCCAGCTGCAGAGCATATTGTGGA GTGCATTGTGGGCATAAGGAAATCTGTTACAAGCTGCCATATTGGCCTGCTTCCGTCCCTGAATCCCTTCCAAC TGTGTAACAGCCCCCTCTAAAAGCGCAAGCCAGTCATACCCCTGTATATCTTAGCAGCACTGAGTCCAGTGCGA ATTTTTCTTGAACTACTGTAATATGTAGATTTTTTGTATTATTGCCAATTTGTGTTACCAGACAATCTGTTAAT GATTTCTCTGTAAGGGCAACGAACGTGCTGGCATCAAAGAATATCAGTTTACATATAACAAGTGTAATAAGA TTCCACCAAAGGACATTCTAAATGTTTTCTTGTTGCTTTAACACTGGAAGATTTAAAGAATAAAAACTCCTGCA TTACTGATTTCTGTGTGGACTGAGTACATTCAGCTGACGAATTTAGTTCCCAGGAAGATGGATTGATGTTCACT AAAAAA

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FIGURE 74

MYLSRSLSIHALWVTVSSVMQPYPLVWGHYDLCKTQIYTEEGKVWDYMACQPESTDMTKYLK VKLDPPDITCGDPPETFCAMGNPYMCNNECDASTPELAHPPELMFDFEGRHPSTFWQSATWK EYPKPLQVNITLSWSKTIELTDNIVITFESGRPDQMILEKSLDYGRTWQPYQYYATDCLDAF HMDPKSVKDLSQHTVLEIICTEEYSTGYTTNSKIIHFEIKDRFALFAGPRLRNMASLYGQLD TTKKLRDFFTVTDLRIRLLRPAVGEIFVDELHLARYFYAISDIKVRGRCKCNLHATVCVYDN SKLTCECEHNTTGPDCGKCKKNYQGRPWSPGSYLPIPKGTANTCIPSISSIGTNVCDNELLH CQNGGTCHNNVRCLCPAAYTGILCEKLRCEEAGSCGSDSGQGAPPHGTPALLLLTTLLGTAS PLVF

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FIGURE 75

CCCACGCGTCCGGGTGACCTGGGCCGAGCCCTCCCGGTCGGCTAAGATTGCTGAGGAGGCGG CGGGTAGCTGGCAGGCGCCGACTTCCGAAGGCCGCCGTCCGGGCGAGGTGTCCTCATGACTT CTCTTGTGGACCATGTCCGTGATCTTTTTTGCCTGCGTGGTACGGGTAAGGGATGGACTGCC CCTCTCAGCCTCTACTGATTTTTACCACACCCAAGATTTTTTGGAATGGAGGAGACGGCTCA AGAGTTTAGCCTTGCGACTGGCCCAGTATCCAGGTCGAGGTTCTGCAGAAGGTTGTGACTTT AGTATACATTTTTCTTCTTCGGGGACGTGGCCTGCATGGCTATCTGCTCCTGCCAGTGTCC AGCAGCCATGGCCTTCTGCTTCCTGGAGACCCTGTGGTGGGAATTCACAGCTTCCTATGACA CTACCTGCATTGGCCTAGCCTCCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTCAG AAAGTGAAGTGCATTTTAACTATGTAAGTTCCTCTCAGATGGAGTGCAGCTTGGAAAAAAT TCAGGAGGAGCTCAAGTTGCAGCCTCCAGCGGTTCTCACTCTGGAGGACACAGATGTGGCAA ATGGGGTGATGAATGGTCACACCCGATGCACTTGGAGCCTGCTCCTAATTTCCGAATGGAA CCAGTGACAGCCCTGGGTATCCTCTCCCTCATTCTCAACATCATGTGTGCTGCCCTGAATCT CATTCGAGGAGTTCACCTTGCAGAACATTCTTTACAGGATCCAAGGAGCTGGTTCTGCTGGT TGGACCAAACCTCGTGAGCCAGCCACCCCTGACCCAAATGAGGAGAGCTCTGATTCTCCCAT CCGGGAGCAGTGATGTCAAACTTCTGCTGCTGGGGAAATCTCATCAGCAGGGAGCCTGTGGA AAAGGCCATGTCAGTGAAATCTGGGAATGGCTGGATTCGGAAACATCTGCCCATGTGTATTG ATGGCAGAGCTGTTGCCCACAAGCGCCTTTTATTTAGGGTAAAATTAACAAATCCATTCTAT TCCTCTGACCCATGCTTAGTACATATGACCTTTAACCCTTACATTTATATGATTCTGGGGTT GCTTCAGAAGTGTTATTTCATGAATCATTCATATGATTTGATCCCCCAGGATTCTATTTTGT TTAATGGGCTTTTCTACTAAAAGCATAAAATACTGAGGCTGATTTAGTCAGGGCAAAACCAT TTACTTTACATATTCGTTTTCAATACTTGCTGTTCATGTTACACAAGCTTCTTACGGTTTTC TTGTAACAATAATATTTTGAGTAAATAATGGGTACATTTTAACAAACTCAGTAGTACAACC TAAACTTGTATAAAAGTGTGTAAAAATGTATAGCCATTTATATCCTATGTATAAATTAAATG AAAAG

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FIGURE 76

MSVIFFACVVRVRDGLPLSASTDFYHTQDFLEWRRRLKSLALRLAQYPGRGSAEGCDFSIHF SSFGDVACMAICSCQCPAAMAFCFLETLWWEFTASYDTTCIGLASRPYAFLEFDSIIQKVKW HFNYVSSSQMECSLEKIQEELKLQPPAVLTLEDTDVANGVMNGHTPMHLEPAPNFRMEPVTA LGILSLILNIMCAALNLIRGVHLAEHSLQDPRSWFCWLDQTS

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FIGURE 77

TGCTTCCTGGAGACCCTGTGGTGGGAATTCACAGCTTCNTATGACACTACCTGCATTGGCNT
AGCCTCCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTCAGAAAGTGAAGTGCATT
TTAACTATGTAAGTTCCTNTCAGATGGAGTGCAGCTTGGAAAAAATTCAGGAGGAGCTCAAG
TTGCAGCCTCCAGCGGTTCTCANTATGGAGGACACAGATGTGGCAAATGGGGT

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FIGURE 78

CTCAGCGGCGCTTCCTCGTAGCGAGCCTAGTGGCGGGTGTTTGCATTGAAACGTGAGCGCGA CCCGACCTTAAAGAGTGGGGAGCAAAGGGAGGACAGAGCCCTTTAAAACGAGGCGGTGGTG CCTGCCCCTTTAAGGGCGGGGCGTCCGGACGACTGTATCTGAGCCCCAGACTGCCCCGAGTT TCTGTCGCAGGCTGCGAGGAAAGGCCCCTAGGCTGGGTCTGGGTGCTTGGCGGCGGCGGCTT CCTCCCGCTCGTCCTCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTA **TG**GAAGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGC GAGTGTATTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTTCCTGAC CCGCTTCAAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCGTCAACAAGA TTGCGCTCGAGCTGTGCACCTTTACCCTGGCAATTGCCCTGGGTGCTGTCCTGCTCCTGCCC TTCTCCATCATCAGCAATGAGGTGCTGCTCTCCCTGCCTCGGAACTACTACATCCAGTGGCT CAACGGCTCCCTCATCCATGGCCTCTGGAACCTTGTTTTTCTCTTCCCCAACCTGTCCCTCA TCTTCCTCATGCCCTTTGCATATTTCTTCACTGAGTCTGAGGGCTTTGCTGGCTCCAGAAAG GGTGTCCTGGGCCGGGTCTATGAGACAGTGGTGATGTTGATGCTCCTCACTCTGCTGGTGCT AGGTATGGTGTGGGTGGCATCAGCCATTGTGGACAAGAACAAGGCCAACAGAGAGTCACTCT CTGCTCCTGGTGTGTACTCCACTGGGTCTCGCCCGCATGTTCTCCGTCACTGGGAAGCTGCT AGTCAAGCCCCGGCTGCTGGAAGACCTGGAGGAGCAGCTGTACTGCTCAGCCTTTGAGGAGG CTACACAGACAGGTCCTGGCTCTGCAGACACAGAGGGTCCTGCTGGAGAAGAGGCGGAAGGC GCCTGTCTGTGCTCATTGTGGCCATCCACATCCTGGAGCTGCTCATCGATGAGGCTGCCATG CCCCGAGGCATGCAGGGTACCTCCTTAGGCCAGGTCTCCTTCTCCAAGCTGGGCTCCTTTGG TGCCGTCATTCAGGTTGTACTCATCTTTTACCTAATGGTGTCCTCAGTTGTGGGCCTTCTATA GCTCTCCACTCTTCCGGAGCCTGCGGCCCAGATGGCACGACACTGCCATGACGCAGATAATT GGGAACTGTGTCTCCTGGTCCTAAGCTCAGCACTTCCTGTCTTCTCTCGAACCCTGGG ACTGCAGCTGTGCGGGCAGAGCTGATCCGGGCCTTTGGGCTGGACAGACTGCCGCTGCCCGT CTCCGGTTTCCCCCAGGCATCTAGGAAGACCCAGCACCAG<u>TGA</u>CCTCCAGCTGGGGGTGGGA AGGAAAAACTGGACACTGCCATCTGCTGCCTAGGCCTGGAGGGAAGCCCAAGGCTACTTGG ACCTCAGGACCTGGAATCTGAGAGGGTGGCTGGCAGAGGGGAGCCAGAGCCATCTGCACTATT GCATAATCTGAGCCAGAGTTTGGGACCAGGACCTCCTGCTTTTCCATACTTAACTGTGGCCT CAGCATGGGGTAGGGCTGGGTGACTGGGTCTAGCCCCTGATCCCAAATCTGTTTACACATCA ATCTGCCTCACTGCTGTTCTGGGCCATCCCCATAGCCATGTTTACATGATTTGATGTGCAAT CTTGCCTCTGGCCCAGCAGAGCCTAAGCACTGTGCTATCCTGGAGGGGCTTTGGACCACCTG AAAGACCAAGGGGATAGGGAGGAGGAGGCTTCAGCCATCAGCAATAAAGTTGATCCCAGGGA AAAAA

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FIGURE 79

MEAPDYEVLSVREQLFHERIRECIISTLLFATLYILCHIFLTRFKKPAEFTTVDDEDATVNK
IALELCTFTLAIALGAVLLLPFSIISNEVLLSLPRNYYIQWLNGSLIHGLWNLVFLFPNLSL
IFLMPFAYFFTESEGFAGSRKGVLGRVYETVVMLMLLTLLVLGMVWVASAIVDKNKANRESL
YDFWEYYLPYLYSCISFLGVLLLLVCTPLGLARMFSVTGKLLVKPRLLEDLEEQLYCSAFEE
AALTRRICNPTSCWLPLDMELLHRQVLALQTQRVLLEKRRKASAWQRNLGYPLAMLCLLVLT
GLSVLIVAIHILELLIDEAAMPRGMQGTSLGQVSFSKLGSFGAVIQVVLIFYLMVSSVVGFY
SSPLFRSLRPRWHDTAMTQIIGNCVCLLVLSSALPVFSRTLGLTRFDLLGDFGRFNWLGNFY
IVFLYNAAFAGLTTLCLVKTFTAAVRAELIRAFGLDRLPLPVSGFPQASRKTQHQ

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FIGURE 80

GGCTGCCGAGGGAAGGCCCCTTGGGTTGGTCTTGGTTGCTTGGCGGCGGCGGTTCNTCCCC
GCTCGTCCTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTATGGAAGC
ACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGCGAGTGTA
TTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTTCCTGACCCGCTTC
AAGAAGCCTGCTGAGTTCACCACAGTGGATGAAGATGCCACCG

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FIGURE 81

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FIGURE 82

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FIGURE 83

MLLWVILLVLAPVSGQFARTPRPIIFLQPPWTTVFQGERVTLTCKGFRFYSPQKTKWYHRYL GKEILRETPDNILEVQESGEYRCQAQGSPLSSPVHLDFSSEMGFPHAAQANVELLGSSDLLT

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FIGURE 84

CAGAAGAGGGGGCTAGCTAGCTGTCTCTGCGGACCAGGGAGACCCCCGCGCCCCCCGGTGT GAGGCGGCCTCACAGGGCCGGGTGGGCTGGCGAGCCGACGCGGCGGCGGAGGAGGCTGTGAG GAGTGTGTGGAACAGGACCCGGGACAGAGGAACCATGCGCTCCGCAGAACCTGAGCACCTTTT GCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATAAGATCTTG GGGGTGCCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAAACTAGCCCTGCA GCTTCATCCCGACCGGAACCCTGATGATCCACAAGCCCAGGAGAAATTCCAGGATCTGGGTG CTGCTTATGAGGTTCTGTCAGATAGTGAGAAACGGAAACAGTACGATACTTATGGTGAAGAA GGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTCACACTTCTTTGGGGATTT TGGTTTCATGTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATATTCCAAGAGGAAGTGATA TTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAGGAAATTTTTGTGGAAGTAGTT AGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGAAGTGCAATTGTCGGCAAGAGAT GCGGACCACCCAGCTGGGCCCTGGGCGCTTCCAAATGACCCAGGAGGTGGTCTGCGACGAAT GCCCTAATGTCAAACTAGTGAATGAAGAACGAACGCTGGAAGTAGAAATAGAGCCTGGGGTG AGAGACGCATGGAGTACCCCTTTATTGGAGAAGGTGAGCCTCACGTGGATGGGGAGCCTGG TGTACACAAATGTGACAATCTCATTAGTTGAGTCACTGGTTGGCTTTGAGATGGATATTACT CACTTGGATGGTCACAAGGTACATATTTCCCGGGATAAGATCACCAGGCCAGGAGCGAAGCT ATGGAAGAAGGGGAAGGGCTCCCCAACTTTGACAACAACAATATCAAGGGCTCTTTGATAA TCACTTTTGATGTGGATTTTCCAAAAGAACAGTTAACAGAGGAAGCGAGAGGAAGGTATCAAA CAGCTACTGAAACAAGGGTCAGTGCAGAAGGTATACAATGGACTGCAAGGATAT**TGA**GAGTG TCATCATGAAATGAATAAGAGGGCTTAAGAATTTGTCCATTTGCATTCGGAAAAGAATGACC AGCAAAAGGTTTACTAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCCTGAGT TTCAAGAATTAAAGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGA GTTGTTAGCAATTTCATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTTG TTATTTTA

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FIGURE 85

MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRSASIKDIKKAYRKLALQLHPDRNPDDPQ
AQEKFQDLGAAYEVLSDSEKRKQYDTYGEEGLKDGHQSSHGDIFSHFFGDFGFMFGGTPRQQ
DRNIPRGSDIIVDLEVTLEEVYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTTQLGPGRFQ
MTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGMEYPFIGEGEPHVDGEPGDLRFRIKVVKH
PIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVHISRDKITRPGAKLWKKGEGLPNFD
NNNIKGSLIITFDVDFPKEQLTEEAREGIKQLLKQGSVQKVYNGLQGY

Important features:

Signal peptide:

amino acids 1-22

Cell attachment sequence.

amino acids 254-257

Nt-dnaJ domain signature.

amino acids 67-87

Homologous region to Nt-dnaJ domain proteins.

amino acids 26-58

N-glycosylation site.

amino acids 5-9, 261-265

Tyrosine kinase phosphorylation site.

amino acids 253-260

N-myristoylation site.

amino acids 18-24, 31-37, 93-99, 215-221

Amidation site.

amino acids 164-168

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FIGURE 86

TGGGACCAGGGAACCCCGGGCCCCCCGGTGGAGNGCCTAACAGGCCGGTGGNTGCGACCGAA
GCGGCGGGGGGAGGAGGTTTTGAGGATTTTTGGAACAGGACCCGGACAGAGGAACCATGGTT
CCGCAGAACNTGAGCACNTTTTGCCTGTTGNTGNTATACTTCATCGGGGCGGTGATTGCCGG
ACGAGATTTNTATAAGATTTTGGGGTGCCTNGAAGTGCCTTNTATAAAAGGATATTAAAAAGG
CCTATAGGAAACTAGCCCTGCAGNTTTATCCCGACCGGAACCCTGATGATCCACAAGCCCAG
GAGAAATTCCAGGATTTGGGTGCTGCTTATGAGGTTNTGTCAGATAGTGAGAAACGGAAACA
GTACGATAATTATGGTGAAGAAGGATTAAAAGATGGTNATCAGAGCTCCCATGGAGACATTT
TTTCACACTTNTTTGGGGGATTTTGGTTTCATGTTTGGAGGAACCCCTNGTCAGCAAGACAGA
AATATTCCAAGAG

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FIGURE 87

GGCACGAGGCGGGGGCAGTCGCGGGATGCGCCCGGGAGCCACAGCCTGAGGCCCTCAGGT CTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTTGCCACTTCCA GCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAAGCATG AGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGTTTGCAGCC TTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGGCCGCGAGACCTGCTGCAGCGCTATGATTC TAAGCCCATTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCTCTGAGTTAGAAC TGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGAATGAAGACTGGATC GAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGATTTGTCACACTCTGAC AGAGAAGCTTGTTGCCATGACAATGGGCTCTGGGGCCAAGATGAAGACTTCAGCCAGTGTCA GCGACATCATTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGGATGATGTTGTGAAGTCGATG TCACCTGGTGCTGGCAAAGGAATGCCTGCCATCTGACGGAGGCCTGGACTGGATTGACC AGTCTCTGTCGGCTGCTGAGGAGCATTTGGAAGTCCTTCGAGAAGCAGCCCTAGCTTCTGAG CCAGATAAAGGCCTCCCAGGCCCTGAAGGCTTCCTGCAGGAGCAGTCTGCAATT**TAG**TGCCT ACAGGCCAGCAGCTAGCCATGAAGGCCCCTGCCGCCATCCCTGGATGGCTCAGCTTAGCCTT TAAAGCAGGAGATCCCCGTCAGTTTATGCCTCTTTTGCAGTTGCAAACTGTGGCTGGTGAGT GGCAGTCTAATACTACAGTTAGGGGAGATGCCATTCACTCTCTGCAAGAGGAGTATTGAAAA CTGGTGGACTGTCAGCTTTATTTAGCTCACCTAGTGTTTTCAAGAAAATTGAGCCACCGTCT AAGAAATCAAGAGGTTTCACATTAAAATTAGAATTTCTGGCCTCTCTCGATCGGTCAGAATG GGTCCCTGAGGCGTCTGGGTCTCTCCTCTCCCTTGCAGGTTTGGGTTTGAAGCTGAGGAACT

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FIGURE 88

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPSEL ELDDVVITNPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMKTSAS VSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLLSVSHLVLVTRNACHLTGGLDWI DQSLSAAEEHLEVLREAALASEPDKGLPGPEGFLQEQSAI

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FIGURE 89

GCTTCATTTCTCCCGACTCAGCTTCCCACCCTGGGCTTTCCGAGGTGCTTTCGCCGCTGTCC CCACCACTGCAGCCATGATCTCCTTAACGGACACGCAGAAAATTGGAATGGGATTAACAGGA TTTGGAGTGTTTTTCCTGTTCTTTGGAATGATTCTCTTTTTTGACAAAGCACTACTGGCTAT TCTTCTTCCAAAAACATAAAATGAAAGCTACAGGTTTTTTTCTGGGTGGTGTATTTGTAGTC CTTATTGGTTGGCCTTTGATAGGCATGATCTTCGAAATTTATGGATTTTTTCTCTTGTTCAG GGGCTTCTTTCCTGTCGTTGTTGGCTTTATTAGAAGAGTGCCAGTCCTTGGATCCCTCCTAAAT TTACCTGGAATTAGATCATTTGTAGATAAAGTTGGAGAAAGCAACAATATGGTA**TAA**CAACA AGTGAATTTGAAGACTCATTTAAAATATTGTGTTATTATAAAGTCATTTGAAGAATATTCA GCACAAAATTAAATTACATGAAATAGCTTGTAATGTTCTTTACAGGAGTTTAAAACGTATAG CCTACAAAGTACCAGCAGCAAATTAGCAAAGAAGCAGTGAAAACAGGCTTCTACTCAAGTGA ACTAAGAAGTCAGCAAGCAAACTGAGAGAGGTGAAATCCATGTTAATGATGCTTAAGAA ACTCTTGAAGGCTATTTGTGTTGTTTTTCCACAATGTGCGAAACTCAGCCATCCTTAGAGAA CTGTGGTGCCTGTTTCTTTTTTTTTTTTTGAAGGCTCAGGAGCATCCATAGGCATTTGCT TTTTAGAAGTGTCCACTGCAATGGCAAAAATATTTCCAGTTGCACTGTATCTCTGGAAGTGA TGCATGAATTCGATTGGATTGTCATTTTAAAGTATTAAAACCAAGGAAACCCCAATTTTG ATGTATGGATTACTTTTTTTTTGNGCNCAGGGCC

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FIGURE 90

MISLTDTQKIGMGLTGFGVFFLFFGMILFFDKALLAIGNVLFVAGLAFVIGLERTFRFFFQK HKMKATGFFLGGVFVVLIGWPLIGMIFEIYGFFLLFRGFFPVVVGFIRRVPVLGSLLNLPGI RSFVDKVGESNNMV

Important features:

Transmembrane domains:

amino acids 12-30 (typeII), 33-52, 69-89 and 93-109

N-myristoylation sites.

amino acids 11-16, 51-56 and 116-121

Aminoacyl-transfer RNA synthetases class-II protein.

amino acids 49-59

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FIGURE 91

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FIGURE 92

GGCACGAGGCTGAACCCAGCCGGCTCCATCTCAGCTTCTGGTTTCTAAGTCCATGTGCCAAA CTGTGGGTAGTTATTTATTTCTGAATAAGAGCGTCCACGCATCATGGACCTCGCGGGACTGC TGAAGTCTCAGTTCCTGTGCCACCTGGTCTTCTGCTACGTCTTTATTGCCTCAGGGCTAATC ATCAACACCATTCAGCTCTTCACTCTCCTCTCTGGCCCATTAACAAGCAGCTCTTCCGGAA GATCAACTGCAGACTGTCCTATTGCATCTCAAGCCAGCTGGTGATGCTGCTGGAGTGGTGGT GCCATCGTGGTTCTCAACCACAAGTTTGAAATTGACTTTCTGTGTGGCTGGAGCCTGTCCGA TTATCGGCTGGATGTGGTACTTCACCGAGATGGTCTTCTGTTCGCGCAAGTGGGAGCAGGAT CGCAAGACGGTTGCCACCAGTTTGCAGCACCTCCGGGACTACCCCGAGAAGTATTTTTTCCT GATTCACTGTGAGGGCACACGGTTCACGGAGAAGAAGCATGAGATCAGCATGCAGGTGGCCC GGGCCAAGGGGCTGCCTCGCCTCAAGCATCACCTGTTGCCACGAACCAAGGGCTTCGCCATC ACCGTGAGGAGCTTGAGAAATGTAGTTTCAGCTGTATATGACTGTACACTCAATTTCAGAAA TTAGGAGGATCCCACTGGAAGACATCCCTGAAGACGATGACGAGTGCTCGGCCTGGCTGCAC AAGCTCTACCAGGAGAAGGATGCCTTTCAGGAGGAGTACTACAGGACGGCCACCTTCCCAGA GACGCCCATGGTGCCCCCCGGCGGCCCTGGACCCTCGTGAACTGGCTGTTTTGGGCCTCGC TGGTGCTCTACCCTTTCTTCCAGTTCCTGGTCAGCATGATCAGGAGCGGGTCTTCCCTGACG **GACTCAGGGAGGTGTCACCATCCGAAGGGAACCTTGGGGAACTGGTGGCCTCTGCATATCCT** CCTTAGTGGGACACGGTGACAAAGGCTGGGTGAGCCCCTGCTGGGCACGGCGGAAGTCACGA CCTCTCCAGCCAGGGAGTCTGGTCTCAAGGCCGGATGGGGAGGAAGATGTTTTGTAATCTTT TGTGTGGTGAGTGTGAACTTTGTTCTGTGATCATAGAAAGGGTATTTTAGGCTGCAGGGGAG GGCAGGGCTGGGGACCGAAGGGGACAAGTTCCCCTTTCATCCTTTGGTGCTGAGTTTTCTGT AACCCTTGGTTGCCAGAGATAAAGTGAAAAGTGCTTTAGGTGAGATGACTAAATTATGCCTC

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FIGURE 93

MDLAGLLKSQFLCHLVFCYVFIASGLIINTIQLFTLLLWPINKQLFRKINCRLSYCISSQLV
MLLEWWSGTECTIFTDPRAYLKYGKENAIVVLNHKFEIDFLCGWSLSERFGLLGGSKVLAKK
ELAYVPIIGWMWYFTEMVFCSRKWEQDRKTVATSLQHLRDYPEKYFFLIHCEGTRFTEKKHE
ISMQVARAKGLPRLKHHLLPRTKGFAITVRSLRNVVSAVYDCTLNFRNNENPTLLGVLNGKK
YHADLYVRRIPLEDIPEDDDECSAWLHKLYQEKDAFQEEYYRTGTFPETPMVPPRRPWTLVN
WLFWASLVLYPFFQFLVSMIRSGSSLTLASFILVFFVASVGVRWMIGVTEIDKGSAYGNSDS
KQKLND

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FIGURE 94

CTGAGGCGGCGGTAGCATGGAGGGGGAGAGTACGTCGGCGGTGCTCTCGGGCTTTGTGCTCG GCGCACTCGCTTTCCAGCACCTCAACACGGACTCGGACACGGAAGGTTTTCTTCTTGGGGAA GTAAAAGGTGAAGCCAAGAACAGCATTACTGATTCCCAAATGGATGATGTTGAAGTTGTTTA TACAATTGACATTCAGAAATATATTCCATGCTATCAGCTTTTTAGCTTTTATAATTCTTCAG GCGAAGTAAATGAGCAAGCACTGAAGAAAATATTATCAAATGTCAAAAAGAATGTGGTAGGT AAACTTGCAGGAGCATTTTTCAAACCAAGACCTTGTTTTTCTGCTATTAACACCAAGTATAA TAACAGAAAGCTGCTCTACTCATCGACTGGAACATTCCTTATATAAACCTCAAAAAGGACTT TTTCACAGGGTACCTTTAGTGGTTGCCAATCTGGGCATGTCTGAACAACTGGGTTATAAAAC TGTATCAGGTTCCTGTATGTCCACTGGTTTTAGCCGAGCAGTACAAACACACAGCTCTAAAT TTTTTGAAGAAGATGGATCCTTAAAGGAGGTACATAAGATAAATGAAATGTATGCTTCATTA CAAGAGGAATTAAAGAGTATATGCAAAAAAGTGGAAGACAGTGAACAAGCAGTAGATAAACT AGTAAAGGATGTAAACAGATTAAAACGAGAAATTGAGAAAAGGAGGAGCACAGATTCAGG CAGCAAGAGAGAACATCCAAAAAGACCCTCAGGAGAACATTTTTCTTTGTCAGGCATTA CGGACCTTTTTTCCAAATTCTGAATTTCTTCATTCATGTGTTATGTCTTTAAAAAAATAGACA TGTTTCTAAAAGTAGCTGTAACTACAACCACCATCTCGATGTAGTAGACAATCTGACCTTAA TGGTAGAACACACTGACATTCCTGAAGCTAGTCCAGCTAGTACACCACAAATCATTAAGCAT AAAGCCTTAGACTTAGATGACAGATGGCAATTCAAGAGATCTCGGTTGTTAGATACACAAGA CAAACGATCTAAAGCAAATACTGGTAGTAGTAACCAAGATAAAGCATCCAAAATGAGCAGCC CAGAAACAGATGAAGAATTGAAAAGATGAAGGGTTTTTGGTGAATATTCACGGTCTCCTACA TTT<u>TGA</u>TCCTTTTAACCTTACAAGGAGATTTTTTTATTTGGCTGATGGGTAAAGCCAAACAT TTCTATTGTTTTACTATGTTGAGCTACTTGCAGTAAGTTCATTTGTTTTACTATGTTCAC CTGTTTGCAGTAATACACAGATAACTCTTAGTGCATTTACTTCACAAAGTACTTTTTCAAAC ATCAGATGCTTTTATTTCCAAACCTTTTTTTCACCTTACTAAGTTGTTGAGGGGAAGGCT TACACAGACACATTCTTTAGAATTGGAAAAGTGAGACCAGGCACAGTGGCTCACACCTGTAA TGGGCAACGTATTGAGACCATGTCTATTAAAAAATAAAATGGAAAAGCAAGAATAGCCTTAT TTTCAAAATATGGAAAGAAATTTATATGAAAATTTATCTGAGTCATTAAAATTCTCCTTAAG TGATACTTTTTTAGAAGTACATTATGGCTAGAGTTGCCAGATAAAATGCTGGATATCATGCA

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FIGURE 95

MEGESTSAVLSGFVLGALAFQHLNTDSDTEGFLLGEVKGEAKNSITDSQMDDVEVVYTIDIQ
KYIPCYQLFSFYNSSGEVNEQALKKILSNVKKNVVGWYKFRRHSDQIMTFRERLLHKNLQEH
FSNQDLVFLLLTPSIITESCSTHRLEHSLYKPQKGLFHRVPLVVANLGMSEQLGYKTVSGSC
MSTGFSRAVQTHSSKFFEEDGSLKEVHKINEMYASLQEELKSICKKVEDSEQAVDKLVKDVN
RLKREIEKRRGAQIQAAREKNIQKDPQENIFLCQALRTFFPNSEFLHSCVMSLKNRHVSKSS
CNYNHHLDVVDNLTLMVEHTDIPEASPASTPQIIKHKALDLDDRWQFKRSRLLDTQDKRSKA
NTGSSNQDKASKMSSPETDEEIEKMKGFGEYSRSPTF

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FIGURE 96

CCAAGCAGCGCGCGCGCCGCCGCCGCCCCCCCCTCTGCGGTCCCCGCGCGCCCTTCCCCT CCTTCCCCGCGTCCCCGCCTCGCCGGCCAGTCAGCTTGCCGGGGTTCGCTGCCCCGCGAAACCCCGAGGTCACCA GGGGACCGTTGCCTGACGCGAGGCCCAGCTCTACTTTTCGCCCCGCGTCTCCTCCGCCTGCTCGCCTCTTCCAC CAACTCCAACTCCTTCTCCCTCCAGCTCCACTCGCTAGTCCCCGACTCCGCCAGCCCTCGGCCCGCTGCCGTAG CGCCGCTTCCCGTCCGGTCCCAAAGGTGGGAACGCGTCCGCCCCGGCCCGCACCATGGCACGGTTCGGCTTGCC AAGTGCGACGTCTTTACGTGTCCAAAGGCTTCAACAAGAACGATGCCCCCCTCCACGAGATCAACGGTGATCAT TTGAAGATCTGTCCCCAGGGTTCTACCTGCTGCTCTCAAGAGATGGAGGAGAAGTACAGCCTGCAAAGTAAAGA TGATTTCAAAAGTGTGGTCAGCGAACAGTGCAATCATTTGCAAGCTGTCTTTGCTTCACGTTACAAGAAGTTTG ATGAATTCTTCAAAGAACTACTTGAAAATGCAGAGAAATCCCTGAATGATATGTTTGTGAAGACATATGGCCAT TTATACATGCAAAATTCTGAGCTATTTAAAGATCTCTTCGTAGAGTTGAAACGTTACTACGTGGTGGGAAATGT GAACCTGGAAGAAATGCTAAATGACTTCTGGGCTCGCCTCCTGGAGCGGATGTTCCGCCTGGTGAACTCCCAGT ACCACTTTACAGATGAGTATCTGGAATGTGTGAGCAAGTATACGGAGCAGCTGAAGCCCTTCGGAGATGTCCCT CGCAAATTGAAGCTCCAGGTTACTCGTGCTTTTGTAGCAGCCCGTACTTTCGCTCAAGGCTTAGCGGTTGCGGG AGATGTCGTGAGCAAGGTCTCCGTGGTAAACCCCACAGCCCAGTGTACCCATGCCCTGTTGAAGATGATCTACT GCTCCCACTGCCGGGGTCTCGTGACTGTGAAGCCATGTTACAACTACTGCTCAAACATCATGAGAGGCTGTTTG GCCAACCAAGGGGATCTCGATTTTGAATGGAACAATTTCATAGATGCTATGCTGATGGTGGCAGAGAGGCTAGA GGGTCCTTTCAACATTGAATCGGTCATGGATCCCATCGATGTGAAGATTTCTGATGCTATTATGAACATGCAGG ATAATAGTGTTCAAGTGTCTCAGAAGGTTTTCCAGGGATGTGGACCCCCCAAGCCCCTCCCAGCTGGACGAATT AGCTGGCACTAGTTTGGACCGACTGGTTACTGATGTCAAGGAGAAACTGAAACAGGCCAAGAAATTCTGGTCCT CCCTTCCGAGCAACGTTTGCAACGATGAGAGGATGGCTGCAGGAAACGGCAATGAGGATGACTGTTGGAATGGG AAAGGCAAAAGCAGGTACCTGTTTGCAGTGACAGGAAATGGATTAGCCAACCAGGGCAACAACCCAGAGGTCCA GGTTGACACCAGCAAACCAGACATACTGATCCTTCGTCAAATCATGGCTCTTCGAGTGATGACCAGCAAGATGA GGCTGTGAGTATCAGCAGTGCCCTTCAGAGTTTGACTACAATGCCACTGACCATGCTGGGAAGAGTGCCAATGA GAAAGCCGACAGTGCTGGTGTCCTGGGGCACAGGCCTACCTCCTCACTGTCTTCTGCATCTTGTTCCTGG TTATGCAGAGAGAGTGGAGA<u>TAA</u>TTCTCAAACTCTGAGAAAAAGTGTTCATCAAAAAGTTAAAAGGCACCAGTT CACTGGTTTAAGAAGTGCTGACTTTGTTTTCTCATTCAGTTTTGGGAGGAAAAGGGACTGTGCATTGAGTTGGT CGCCTTGTTTCTTACAAGCAAACCAGGGTCCCTTCTTGGCACGTAACATGTACGTATTTCTGAAATATTAAATA GCTGTACAGAAGCAGGTTTTATTTATCATGTTATCTTATTAAAAAGAAAAAGCCCAAAAAGC

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FIGURE 97

MARFGLPALLCTLAVLSAALLAAELKSKSCSEVRRLYVSKGFNKNDAPLHEINGDHLKICPQ
GSTCCSQEMEEKYSLQSKDDFKSVVSEQCNHLQAVFASRYKKFDEFFKELLENAEKSLNDMF
VKTYGHLYMQNSELFKDLFVELKRYYVVGNVNLEEMLNDFWARLLERMFRLVNSQYHFTDEY
LECVSKYTEQLKPFGDVPRKLKLQVTRAFVAARTFAQGLAVAGDVVSKVSVVNPTAQCTHAL
LKMIYCSHCRGLVTVKPCYNYCSNIMRGCLANQGDLDFEWNNFIDAMLMVAERLEGPFNIES
VMDPIDVKISDAIMNMQDNSVQVSQKVFQGCGPPKPLPAGRISRSISESAFSARFRPHHPEE
RPTTAAGTSLDRLVTDVKEKLKQAKKFWSSLPSNVCNDERMAAGNGNEDDCWNGKGKSRYLF
AVTGNGLANQGNNPEVQVDTSKPDILILRQIMALRVMTSKMKNAYNGNDVDFFDISDESSGE
GSGSGCEYQQCPSEFDYNATDHAGKSANEKADSAGVRPGAQAYLLTVFCILFLVMQREWR

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FIGURE 98

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FIGURE 99

MKVLISSLLLLLPLMLMSMVSSSLNPGVARGHRDRGQASRRWLQEGGQECECKDWFLRAPRR KFMTVSGLPKKQCPCDHFKGNVKKTRHQRHHRKPNKHSRACQQFLKQCQLRSFALPL

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FIGURE 100

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FIGURE 101

MAVLVLRLTVVLGLLVLFLTCYADDKPDKPDDKPDDSGKDPKPDFPKFLSLLGTEIIENAVE FILRSMSRSTGFMEFDDNEGKHSSK

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FIGURE 102

GGACGCCAGCGCCTGCAGAGGCTGAGCAGGGAAAAAGCCAGTGCCCCAGCGGAAGCACAGCT CAGAGCTGGTCTGCCATCGGACATCCTGGTCCCACTCCTGCAGCTGCTGCTGCTTCTTAC CCTGCCCCTGCACCTCATGGCTCTGCTGGGCTGCTGGCAGCCCCTGTGCAAAAGCTACTTCC CCTACCTGATGGCCGTGCTGACTCCCAAGAGCAACCGCAAGATGGAGAGCAAGAAACGGGAG CTCTTCAGCCAGATAAAGGGGCTTACAGGAGCCTCCGGGAAAGTGGCCCTACTGGAGCTGGG CTGCGGAACCGGAGCCAACTTTCAGTTCTACCCACCGGGCTGCAGGGTCACCTGCCTAGACC CAAATCCCCACTTTGAGAAGTTCCTGACAAAGAGCATGGCTGAGAACAGGCACCTCCAATAT GGAGAGTACTGAGACCGGGAGGTGTGCTCTTTTTCTGGGAGCATGTGGCAGAACCATATGGA AGCTGGGCCTTCATGTGGCAGCAAGTTTTCGAGCCCACCTGGAAACACATTGGGGATGGCTG CTGCCTCACCAGAGAGACCTGGAAGGATCTTGAGAACGCCCAGTTCTCCGAAATCCAAATGG AACGACAGCCCCTCCCTTGAAGTGGCTACCTGTTGGGCCCCACATCATGGGAAAGGCTGTC AAACAATCTTTCCCAAGCTCCAAGGCACTCATTTGCTCCTTCCCCAGCCTCCAATTAGAACA AGCCACCCACCAGCCTATCTATCTTCCACTGAGAGGGACCTAGCAGAATGAGAGAAGACATT CATGTACCACCTACTAGTCCCTCTCCCCAACCTCTGCCAGGGCAATCTCTAACTTCAATC CCGCCTTCGACAGTGAAAAAGCTCTACTTCTACGCTGACCCAGGGAGGAAACACTAGGACCC TGTTGTATCCTCAACTGCAAGTTTCTGGACTAGTCTCCCAACGTTTGCCTCCCAATGTTGTC CCTTTCCTTCGTTCCCATGGTAAAGCTCCTCTCGCTTTCCTCCTGAGGCTACACCCATGCGT CTCTAGGAACTGGTCACAAAAGTCATGGTGCCTGCATCCCTGCCAAGCCCCCTGACCCTCT CTCCCACTACCACCTTCTTCCTGAGCTGGGGGCACCAGGGAGAATCAGAGATGCTGGGGAT **AACCACG**

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FIGURE 103

MDILVPLLQLLVLLLTLPLHLMALLGCWQPLCKSYFPYLMAVLTPKSNRKMESKKRELFSQI KGLTGASGKVALLELGCGTGANFQFYPPGCRVTCLDPNPHFEKFLTKSMAENRHLQYERFVV APGEDMRQLADGSMDVVVCTLVLCSVQSPRKVLQEVRRVLRPGGVLFFWEHVAEPYGSWAFM WQQVFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKWLPVGPHIMGKAVKQSFP SSKALICSFPSLQLEQATHQPIYLPLRGT

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FIGURE 104

GTGGGATTTATTTGAGTGCAAGATCGTTTTCTCAGTGGTGGTGGAAGTTGCCTCATCGCAGG CAGATGTTGGGGCTTTGTCCGAACAGCTCCCCTCTGCCAGCTTCTGTAGATAAGGGTTAAAA ACTAATATTTATATGACAGAAGAAAAAGATGTCATTCCGTAAAGTAAACATCATCTTGG TCCTGGCTGTTGCTCTTCTTACTGGTTTTGCACCATAACTTCCTCAGCTTGAGCAGTTTG TTAAGGAATGAGGTTACAGATTCAGGAATTGTAGGGCCTCAACCTATAGACTTTGTCCCAAA TGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCCTGTGGTCATCGCTGCATCTG AAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTCAGCACAACACTCGCTCCAAT GTGATTTTCTACATTGTTACTCTCAACAATACAGCAGACCATCTCCGGTCCTGGCTCAACAG AAGTAAAGGAGGATCCTGACCAGGGGGAATCCATGAAACCTTTAACCTTTGCAAGGTTCTAC TTGCCAATTCTGGTTCCCAGCGCAAAGAAGGCCATATACATGGATGATGATGTAATTGTGCA AGGTGATATTCTTGCCCTTTACAATACAGCACTGAAGCCAGGACATGCAGCTGCATTTTCAG AAGATTGTGATTCAGCCTCTACTAAAGTTGTCATCCGTGGAGCAGGAAACCAGTACAATTAC ATTGGCTATCTTGACTATAAAAAGGAAAGAATTCGTAAGCTTTCCATGAAAGCCAGCACTTG CTCATTTAATCCTGGAGTTTTTGTTGCAAACCTGACGGAATGGAAACGACAGAATATAACTA ACCAACTGGAAAAATGGATGAAACTCAATGTAGAAGAGGGACTGTATAGCAGAACCCTGGCT GGTAGCATCACAACACCTCCTCTGCTTATCGTATTTTATCAACAGCACTCTACCATCGATCC TATGTGGAATGTCCGCCACCTTGGTTCCAGTGCTGGAAAACGATATTCACCTCAGTTTGTAA AGGCTGCCAAGTTACTCCATTGGAATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATAT ACTGATGTTTGGGAAAAATGGTATATTCCAGACCCAACAGGCAAATTCAACCTAATCCGAAG ATATACCGAGATCTCAAACATAAAG**TGA**AACAGAATTTGAACTGTAAGCAAGCATTTCTCAG GAAGTCCTGGAAGATAGCATGCATGGGAAGTAACAGTTGCTAGGCTTCAATGCCTATCGGTA GCAAGCCATGGAAAAAGATGTCTCAGCTAGGTAAAGATGACAAACTGCCCTGTCTGGCAGTC AGCTTCCCAGACAGACTATAGACTATAAATATGTCTCCATCTGCCTTACCAAGTGTTTTCTT ACATTTTTC

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FIGURE 105

MSFRKVNIIILVLAVALFLLVLHHNFLSLSSLLRNEVTDSGIVGPQPIDFVPNALRHAVDGR QEEIPVVIAASEDRLGGAIAAINSIQHNTRSNVIFYIVTLNNTADHLRSWLNSDSLKSIRYK IVNFDPKLLEGKVKEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIVQGDILALYNT ALKPGHAAAFSEDCDSASTKVVIRGAGNQYNYIGYLDYKKERIRKLSMKASTCSFNPGVFVA NLTEWKRQNITNQLEKWMKLNVEEGLYSRTLAGSITTPPLLIVFYQQHSTIDPMWNVRHLGS SAGKRYSPQFVKAAKLLHWNGHLKPWGRTASYTDVWEKWYIPDPTGKFNLIRRYTEISNIK

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FIGURE 106

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FIGURE 107

CGACGCTCTAGCGGTTACCGCTGCGGGCTGGCTGGGCGTAGTGGGGCTGCGCGGCTGCCACG TGGGCTCCGGGGCCTGCGCGGGCGCTGAGCTGGCAGGCGGGTCGGGGCGCGGGCTGCA TCCGCATCTCCTCCATCGCCTGCAGTAAGGGCGGCCGCGGGGAGCCTTTGAGGGGAACGACT TGTCGGAGCCCTAACCAGGGGTGTCTCTGAGCCTGGTGGGATCCCCGGAGCGTCACATCACT TTCCGATCACTTCAAAGTGGTTAAAAACTAATATTTATATGACAGAAGAAAAAGATGTCATT CCGTAAAGTAAACATCATCATCTTGGTCCTGGGCTGTTGCTCTTCTTACTGGTTTTGCAC CATAACTTCCTCAGCTTGAGGCAGTTTGTTAAGGAATGAGGTTACAGATTCAGGAATTGTAG GGCCTCAACCTATAGGACTTTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGA GGAGATTCCTGTGGTCATCGCTGCATCTGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAA ACAGCATTCAGCACAACACTCGCTCCAATGTGATTTTCTACATTGTTACTCTCAACAATACA GCAGACCATCTCCGGTCCTGGGCTCAACAGTGATTCCCTGAAAAGCATCAGATACAAAATTG TCAATTTTGACCCTAAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCAGGGGGAATCC ATGAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGGTTCCCAGCGCAAAGAAGG CCATATACATGGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGCA CTGAAGCCAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTCAGCCTCTACTAAAGTTGT CATCCGTGGAGCAGGAAACCAGTACAATTACATTGGCTATCTTGACTATAAAAAGGAAAGAA TTCGTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTTTTGTTGCAAAC CTGACGGAATGGAAACGACAGAATATAACTAACCAACTGGAAAAATGGATGAAACTCAATGT AGAAGAGGGACTGTATAGCAGAACCCTGGCTGGTAGCATCACAACACCTCCTCTGCTTATCG TATTTTATCAACAGCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGGTTCCAGT GCTGGAAAACGATATTCACCTCAGTTTGTAAAGGCTGCCAAGTTACTCCATTGGAATGGACA TTTGAAGCCATGGGGAAGGACTGCTTCATATACTGATGTTTGGGGAAAAATGGTATATTCCA GACCCAACAGGCAAATTCAACCTAATCCGAAGATATACCGAGATCTCAAACATAAAGTGAAA CAGAATTTGAACTGTAAGCAAGCATTTCTCAGGAAGTCCTGGAAGATAGCATGCGTGGGAAG TAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAAGATGTGTCAGCTAG ATGTCTCCATCTGCCTTACCAAGTGTTTTCTTACTACAATGCTGAATGACTGGAAAGAAGAA CTGATATGGCTAGTTCAGCTAGCTGGTACAGATAATTCAAAACTGCTGTTGGTTTTAATTTT AAAAA

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FIGURE 108

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FIGURE 109

MGAAISQGALIAIVCNGLVGFLLLLLWVILCWACHSRLPTLTLSLNPVPTPALAPVLRRPHH PRSPAMKAATCCSPEGPWPSLEPRT

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FIGURE 110

GTTTGAATTCCTTCAACTATACCCACAGTCCAAAAGCAGACTCACTGTGTCCCAGGCTACCA GTTCCTCCAAGCAAGTCATTTCCCTTATTTAACCGATGTGTCCCTCAAACACCTGAGTGCTA CTCCCTATTTGCATCTGTTTTGATAAATGATGTTGACACCCTCCACCGAATTCTAAGTGGAA TCATGTCGGGAAGAGATACAATCCTTGGCCTGTGTATCCTCGCATTAGCCTTGTCTTTGGCC ATGATGTTTACCTTCAGATTCATCACCACCCTTCTGGTTCACATTTTCATTTCATTGGTTAT TTTGGGATTGTTTGTCTGCGGTGTTTTATGGTGGCTGTATTATGACTATACCAACGACC TCCACAGGCATCACGGCAGTGCTCGTCTTGATTTTTGTTCTCAGAAAGAGAATAAAATT GACAGTTGAGCTTTTCCAAATCACAAATAAAGCCATCAGCAGTGCTCCCTTCCTGCTGTTCC AGCCACTGTGGACATTTGCCATCCTCATTTTCTTCTGGGTCCTCTGGGTGGCTGTGCTGCTG AGCCTGGGAACTGCAGGAGCTGCCCAGGTTATGGAAGGCGGCCAAGTGGAATATAAGCCCCT TTCGGGCATTCGGTACATGTGGTCGTACCATTTAATTGGCCTCATCTGGACTAGTGAATTCA TCCTTGCGTGCCAGCAAATGACTATAGCTGGGGCAGTGGTTACTTGTTATTTCAACAGAAGT AGGAACCGTTGTGAAAGGGTCATTTTTAATCTCTGTGGTGAGGATTCCGAGAATCATTGTCA TGTACATGCAAAACGCACTGAAAGAACAGCAGCATGGTGCATTGTCCAGGTACCTGTTCCGA TGCTGCTACTGCTGTTTCTGGTGTCTTGACAAATACCTGCTCCATCTCAACCAGAATGCATA TACTACAACTGCTATTAATGGGACAGATTTCTGTACATCAGCAAAAGATGCATTCAAAATCT TGTCCAAGAACTCAAGTCACTTTACATCTATTAACTGCTTTGGAGACTTCATAATTTTTCTA GGAAAGGTGTTAGTGGTGTTTTCACTGTTTTTGGAGGACTCATGGCTTTTAACTACAATCG GGCATTCCAGGTGTGGGCAGTCCCTCTGTTATTGGTAGCTTTTTTTGCCTACTTAGTAGCCC ATAGTTTTTTATCTGTGTTTGAAACTGTGCTGGATGCACTTTTCCTGTGTTTTGCTGTTGAT CTGGAAACAATGATGGATCGTCAGAAAAGCCCTACTTTATGGATCAAGAATTTCTGAGTTT CGTAAAAAGGAGCAACAAATTAAACAATGCAAGGGCACAGCAGGACAAGCACTCATTAAGGA ATGAGGAGGGAACAGAACTCCAGGCCATTGTGAGATACCATTTAGGTATCTGTACCT GGAAAACATTTCCTTCTAAGAGCCATTTACAGAATAGAAGATGAGACCACTAGAGAAAAGTT AGTGAATTTTTTTTTAAAAGACCTAATAAACCCTATTCTTCCTCAAAA

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FIGURE 111

MSGRDTILGLCILALALSLAMMFTFRFITTLLVHIFISLVILGLLFVCGVLWWLYYDYTNDL
SIELDTERENMKCVLGFAIVSTGITAVLLVLIFVLRKRIKLTVELFQITNKAISSAPFLLFQ
PLWTFAILIFFWVLWVAVLLSLGTAGAAQVMEGGQVEYKPLSGIRYMWSYHLIGLIWTSEFI
LACQQMTIAGAVVTCYFNRSKNDPPDHPILSSLSILFFYHQGTVVKGSFLISVVRIPRIIVM
YMQNALKEQQHGALSRYLFRCCYCCFWCLDKYLLHLNQNAYTTTAINGTDFCTSAKDAFKIL
SKNSSHFTSINCFGDFIIFLGKVLVVCFTVFGGLMAFNYNRAFQVWAVPLLLVAFFAYLVAH
SFLSVFETVLDALFLCFAVDLETNDGSSEKPYFMDQEFLSFVKRSNKLNNARAQQDKHSLRN
EEGTELQAIVR

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FIGURE 112

GTTCGATTAGCTCCTCTGAGAAGAAGAGAAAAGGTTCTTGGACCTCTCCCTGTTTCTTCCTT TGTGGTGAAAATTTTTTGAAAAAAAATTGCCTTCTTCAAACAAGGGTGTCATTCTGATATT TATCAGGACTGTTGTTCTCACTATGAAGGCATCTGTTATTGAAATGTTCCTTGTTTTTGCTGG TGACTGGAGTACATTCAAACAAAGAAACGGCAAAGAAGATTAAAAGGCCCAAGTTCACTGTG CCTCAGATCAACTGCGATGTCAAAGCCGGAAAGATCATCGATCCTGAGTTCATTGTGAAATG TCCAGCAGGATGCCAAGACCCCAAATACCATGTTTATGGCACTGACGTGTATGCATCCTACT CCAGTGTGTGTGGCGCTGCCGTACACAGTGGTGTGCTTGATAATTCAGGAGGGAAAATACTT GTTCGGAAGGTTGCTGGACAGTCTGGTTACAAAGGGAGTTATTCCAACGGTGTCCAATCGTT ATCCCTACCACGATGGAGAGATCCTTTATCGTCTTAGAAAGTAAACCCAAAAAGGGTGTAA CCTACCCATCAGCTCTTACATACTCATCATCGAAAAGTCCAGCTGCCCAAGCAGGTGAGACC ACAAAAGCCTATCAGAGGCCACCTATTCCAGGGACAACTGCACAGCCGGTCACTCTGATGCA GCTTCTGGCTGTCACTGTAGCTGTGGCCACCCCCACCACCTTGCCAAGGCCATCCCCTTCTG CTGCTTCTACCACCAGCATCCCCAGACCACAATCAGTGGGCCACAGGAGCCAGGAGATGGAT CTCTGGTCCACTGCCACCTACACAAGCAGCCAAAACAGGCCCAGAGCTGATCCAGGTATCCAAAGGCAAGATCCTTCAGGAGCTGCCTTCCAGAAACCTGTTGGAGCGGATGTCAGCCTGGGAC TTGTTCCAAAAGAAGAATTGAGCACACAGTCTTTGGAGCCAGTATCCCTGGGAGATCCAAAC AATTCTCGAGATCTGAAGACAGCCATAGAGAAAATTACTCAGAGAGGAGGACTTTCTAATGT AGGTCGGGCCATCTCCTTTGTGACCAAGAACTTCTTTTCCAAAGCCAATGGAAACAGAAGCG GGGCTCCCAATGTGGTGGTGGTGGTGGATGGCTGCCCACGGACAAAGTGGAGGAGGCT TCAAGACTTGCGAGAGAGTCAGGAATCAACATTTTCTTCATCACCATTGAAGGTGCTGCTGA AAATGAGAAGCAGTATGTGGTGGAGCCCAACTTTGCAAACAAGGCCGTGTGCAGAACAAACG GCTTCTACTCGCTCCACGTGCAGAGCTGGTTTGGCCTCCACAAGACCCTGCAGCCTCTGGTG AAGCGGGTCTGCGACACTGACCGCCTGGCCTGCAGCAAGACCTGCTTGAACTCGGCTGACAT TGGCTTCGTCATCGACGGCTCCAGCAGTGTGGGGACGGGCAACTTCCGCACCGTCCTCCAGT TTGTGACCAACCTCACCAAAGAGTTTGAGATTTCCGACACGGACACGCGCATCGGGGCCGTGCAGTACACCTACGAACAGCGGCTGGAGTTTGGGTTCGACAAGTACAGCAGCAAGCCTGACAT CCTCAACGCCATCAAGAGGGTGGGCTACTGGAGTGGTGGCACCAGCACGGGGGCTGCCATCA ACTTCGCCCTGGAGCAGCTCTTCAAGAAGTCCAAGCCCAACAAGAGGAAGTTAATGATCCTC ATCACCGACGGAGGTCCTACGACGACGTCCGGATCCCAGCCATGGCTGCCCATCTGAAGGGAGGTGATCACCTATGCGATAGGCGTTGCCTGGGCTGCCCAAGAGGAGCTAGAAGTCATTGCCA CTCACCCCGCCAGAGACCACTCCTTCTTTGTGGACGAGTTTGACAACCTCCATCAGTATGTC CCCAGGATCATCCAGAACATTTGTACAGAGTTCAACTCACAGCCTCGGAAC**TGA**ATTCAGAG

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FIGURE 113

MRTVVLTMKASVIEMFLVLLVTGVHSNKETAKKIKRPKFTVPQINCDVKAGKIIDPEFIVKC
PAGCQDPKYHVYGTDVYASYSSVCGAAVHSGVLDNSGGKILVRKVAGQSGYKGSYSNGVQSL
SLPRWRESFIVLESKPKKGVTYPSALTYSSSKSPAAQAGETTKAYQRPPIPGTTAQPVTLMQ
LLAVTVAVATPTTLPRPSPSAASTTSIPRPQSVGHRSQEMDLWSTATYTSSQNRPRADPGIQ
RQDPSGAAFQKPVGADVSLGLVPKEELSTQSLEPVSLGDPNCKIDLSFLIDGSTSIGKRRFR
IQKQLLADVAQALDIGPAGPLMGVVQYGDNPATHFNLKTHTNSRDLKTAIEKITQRGGLSNV
GRAISFVTKNFFSKANGNRSGAPNVVVVMVDGWPTDKVEEASRLARESGINIFFITIEGAAE
NEKQYVVEPNFANKAVCRTNGFYSLHVQSWFGLHKTLQPLVKRVCDTDRLACSKTCLNSADI
GFVIDGSSSVGTGNFRTVLQFVTNLTKEFEISDTDTRIGAVQYTYEQRLEFGFDKYSSKPDI
LNAIKRVGYWSGGTSTGAAINFALEQLFKKSKPNKRKLMILITDGRSYDDVRIPAMAAHLKG
VITYAIGVAWAAQEELEVIATHPARDHSFFVDEFDNLHQYVPRIIQNICTEFNSQPRN

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FIGURE 114

CAGGATGAACTGGTTGCAGTGGCTGCTGCTGCGGGGGGCGCTGAGAGGACACGAGCTCTA TGCCTTTCCGGCTGCTCATCCCGCTCGGCCTCCTGTGCGCGCTGCTGCCTCAGCACCATGGT GCGCCAGGTCCCGACGGCTCCGCCCAGATCCCGCCCACTACAGTTTTTCTCTGACTCTAAT TGATGCACTGGACACCTTGCTGATTTTGGGGAATGTCTCAGAATTCCAAAGAGTGGTTGAAG CGAGTGGTAGGAGGACTCCTGTCTGCTCATCTGCTCTCCAAGAAGGCTGGGGTGGAAGTAGA GGCTGGATGGCCCTGTTCCGGGCCTCTCCTGAGAATGGCTGAGGAGGCGGCCCGAAAACTCC AACCCAGGAGAGACCCCTGTCACCTGTACGGCAGGGATTGGGACCTTCATTGTTGAATTTGC CACCCTGAGCAGCCTCACTGGTGACCCGGTGTTCGAAGATGTGGCCAGAGTGGCTTTGATGC GCCTCTGGGAGAGCCGGTCAGATATCGGGCTGGTCGGCAACCACATTGATGTGCTCACTGGC AAGTGGGTGGCCCAGGACGCAGGCATCGGGGCTGGCGTGGACTCCTACTTTGAGTACTTGGT GAAAGGAGCCATCCTGCTTCAGGATAAGAAGCTCATGGCCATGTTCCTAGAGTATAACAAAG CCATCCGGAACTACACCCGCTTCGATGACTGGTACCTGTGGGTTCAGATGTACAAGGGGACT GTGTCCATGCCAGTCTTCCAGTCCTTGGAGGCCTACTGGCCTGGTCTTCAGAGCCTCATTGG AGACATTGACAATGCCATGAGGACCTTCCTCAACTACTACACTGTATGGAAGCAGTTTGGGG GGCTCCCGGAATTCTACAACATTCCTCAGGGATACACAGTGGAGAAGCGAGAGGGCTACCCA CTTCGGCCAGAACTTATTGAAAGCGCAATGTACCTCTACCGTGCCACGGGGGATCCCACCCT CCTAGAACTCGGAAGAGATGCTGTGGAATCCATTGAAAAAATCAGCAAGGTGGAGTGCGGAT TTGCAACAATCAAAGATCTGCGAGACCACAAGCTGGACAACCGCATGGAGTCGTTCTTCCTG GTCCACCTTCGACGCGGTGATCACCCCCTATGGGGGAGTGCATCCTGGGGGGCTGGGGGGTACA TCTTCAACACAGAAGCTCACCCCATCGACCTTGCCGCCCTGCACTGCTGCCAGAGGCTGAAG GAAGAGCAGTGGGAGGTGGAGGACTTGATGAGGGAATTCTACTCTCAAACGGAGCAGGTC GAAATTTCAGAAAAACACTGTTAGTTCGGGGCCATGGGAACCTCCAGCAAGGCCAGGAACAC CTTCTCAGCTGCCCCAGTCAGCCCTTCACCTCCAAGTTGGCATTACTGGGACAGGTTTTCCT AATTGCTTTTGGCTATCATAAAA

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FIGURE 115

MPFRLLIPLGLLCALLPQHHGAPGPDGSAPDPAHYSFSLTLIDALDTLLILGNVSEFQRVVE
VLQDSVDFDIDVNASVFETNIRVVGGLLSAHLLSKKAGVEVEAGWPCSGPLLRMAEEAARKL
LPAFQTPTGMPYGTVNLLHGVNPGETPVTCTAGIGTFIVEFATLSSLTGDPVFEDVARVALM
RLWESRSDIGLVGNHIDVLTGKWVAQDAGIGAGVDSYFEYLVKGAILLQDKKLMAMFLEYNK
AIRNYTRFDDWYLWVQMYKGTVSMPVFQSLEAYWPGLQSLIGDIDNAMRTFLNYYTVWKQFG
GLPEFYNIPQGYTVEKREGYPLRPELIESAMYLYRATGDPTLLELGRDAVESIEKISKVECG
FATIKDLRDHKLDNRMESFFLAETVKYLYLLFDPTNFIHNNGSTFDAVITPYGECILGAGGY
IFNTEAHPIDLAALHCCQRLKEEQWEVEDLMREFYSLKRSRSKFQKNTVSSGPWEPPARPGT
LFSPENHDQARERKPAKQKVPLLSCPSQPFTSKLALLGQVFLDSS

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FIGURE 116

AAAGTTACATTTCTCTGGAACTCTCCTAGGCCACTCCCTGCTGATGCAACATCTGGGTTTG GGCAGAAAGGAGGTGCTTCGGAGCCCGCCCTTTCTGAGCTTCCTGGGCCGGCTCTAGAACA GAGATGGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCAAACTGAGTCTACCA **AATG**CAGACTTTCACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTCATGTGGTTTTTCT ACGCATTGATTCCATGTTTGCTCACAGATGÁAGTGGCCATTCTGCCTGCCCCTCAGAACCTC TCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTGATCGCGCCTGGAGA AACAGTGTACTATTCTGTCGAATACCAGGGGGAGTACGAGAGCCTGTACACGAGCCACATCT GGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGTGATGTCACTGATGACATC ACGGCCACTGTGCCATACAACCTTCGTGTCAGGGCCACATTGGGCTCACAGACCTCAGCCTG GAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATCCTTACCCGACCTGGGATGGAGA TCACCAAAGATGGCTTCCACCTGGTTATTGAGCTGGAGGACCTGGGGCCCCAGTTTGAGTTC CTTGTGGCCTACTGGAGGAGGGGGCCTGGTGCCGAGGAACATGTCAAAATGGTGAGGAGTGG GGGTATTCCAGTGCACCTAGAAACCATGGAGCCAGGGGCTGCATACTGTGTGAAGGCCCAGA GGAGAGGCCATTCCCCTGGTACTGGCCCTGTTTGCCTTTGTTGGCTTCATGCTGATCCTTGT GGTCGTGCCACTGTTCGTCTGGAAAATGGGCCGGCTGCTCCAGTACTCCTGTTGCCCCGTGG TGGTCCTCCCAGACACCTTGAAAATAACCAATTCACCCCAGAAGTTAATCAGCTGCAGAAGG GAGGAGGTGGATGCCTGTGCCACGGCTGTGATGTCTCCTGAGGAACTCCTCAGGGCCTGGAT CTCATAGGTTTGCGGAAGGGCCCAGGTGAAGCCGAGAACCTGGTCTGCATGACATGGAAACC ATGAGGGGACAAGTTGTGTTTCTGTTTTCCGCCACGGACAAGGGATGAGAAGTAGGAAGA GCCTGTTGTCTACAAGTCTAGAAGCAACCATCAGAGGCAGGGTGGTTTGTCTAACAGAACAC CTGGGAAAAGTGACTTCATCCCTTCGGTCCTAAGTTTTCTCATCTGTAATGGGGGAATTACC TGTTTCTGGAGAGCAGACATAAATGTATGATGAGAATGATCAAGGACTCTACACACTGGGT GGCTTGGAGAGCCCACTTTCCCAGAATAATCCTTGAGAGAAAAGGAATCATGGGAGCAATGG TGTTGAGTTCACTTCAAGCCCAATGCCGGTGCAGAGGGGAATGGCTTAGCGAGCTCTACAGT AGGTGACCTGGAGGAAGGTCACAGCCACACTGAAAATGGGATGTGCATGAACACGGAGGATC TGTTGGTAAAGTACAGAATTCAGCAAATAAAAAGGGCCACCCTGGCCAAAAAGCGGTAAAAAA AAAAAAAAA

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FIGURE 117

MQTFTMVLEEIWTSLFMWFFYALIPCLLTDEVAILPAPQNLSVLSTNMKHLLMWSPVIAPGE TVYYSVEYQGEYESLYTSHIWIPSSWCSLTEGPECDVTDDITATVPYNLRVRATLGSQTSAW SILKHPFNRNSTILTRPGMEITKDGFHLVIELEDLGPQFEFLVAYWRREPGAEEHVKMVRSG GIPVHLETMEPGAAYCVKAQTFVKAIGRYSAFSQTECVEVQGEAIPLVLALFAFVGFMLILV VVPLFVWKMGRLLQYSCCPVVVLPDTLKITNSPQKLISCRREEVDACATAVMSPEELLRAWIS

Important features:

Signal peptide:

amino acids 1-29

Transmembrane domain:

amino acids 230-255

N-glycosylation sites.

amino acids 40-43 and 134-137

Tissue factor proteins homology.

amino acids 92-119

Integrins alpha chain protein homology.

amino acids 232-262

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FIGURE 118

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FIGURE 119

CGGACGCGTGGCCGCCACCTCCGGAACAAGCCATGGTGGCGGCGACGGTGGCAGCGGCGTG GCTGCTCCTGTGGGCTGCGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAGGCGG TCAACATCCGGGGCAAACTGGTGTCGCTGGAGAAGTACCGCGGATCGGTGTCCCTGGTGGTG AATGTGGCCAGCGAGTGCGGCTTCACAGACCAGCACTACCGAGCCCTGCAGCAGCTGCAGCG AGACCTGGGCCCCACCACTTTAACGTGCTCGCCTTCCCCTGCAACCAGTTTGGCCAACAGG AGCCTGACAGCAACAAGGAGATTGAGAGCTTTGCCCGCCGCACCTACAGTGTCTCATTCCCC ATGTTTAGCAAGATTGCAGTCACCGGTACTGGTGCCCATCCTGCCTTCAAGTACCTGGCCCA GACTTCTGGGAAGGAGCCCACCTGGAACTTCTGGAAGTACCTAGTAGCCCCAGATGGAAAGG TGGTAGGGGCTTGGGACCCAACTGTGTCAGTGGAGGAGGTCAGACCCCAGATCACAGCGCTC GTGAGGAAGCTCATCCTACTGAAGCGAGAAGACTTA**TAA**CCACCGCGTCTCCTCCTCCACCA CCTCATCCCGCCCACCTGTGTGGGGCTGACCAATGCAAACTCAAATGGTGCTTCAAAGGGAG AGACCCACTGACTCTCCTTTACTCTTATGCCATTGGTCCCATCATTCTTGTGGGGGAA AAATTCTAGTATTTTGATTATTTGAATCTTACAGCAACAAATAGGAACTCCTGGCCAATGAG AGCTCTTGACCAGTGAATCACCAGCCGATACGAACGTCTTGCCAACAAAAATGTGTGGCAAA TAGAAGTATATCAAGCAATAATCTCCCACCCAAGGCTTCTGTAAACTGGGACCAATGATTAC CTCATAGGGCTGTTGTGAGGATTAGGATGAAATACCTGTGAAAGTGCCTAGGCAGTGCCAGC CAAATAGGAGGCATTCAATGAACATTTTTTGCATATAAACCAAAAAATAACTTGTTATCAAT AAAAACTTGCATCCAACATGAATTTCCAGCCGATGATAATCCAGGCCAAAGGTTTAGTTGTT GTTATTTCCTCTGTATTATTTCTTCATTACAAAAGAAATGCAAGTTCATTGTAACAATCCA AACAATACCTCACGATATAAAATAAAAATGAAAGTATCCTCCTCAAAAA

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FIGURE 120

MVAATVAAAWLLLWAAACAQQEQDFYDFKAVNIRGKLVSLEKYRGSVSLVVNVASECGFTDQ HYRALQQLQRDLGPHHFNVLAFPCNQFGQQEPDSNKEIESFARRTYSVSFPMFSKIAVTGTG AHPAFKYLAQTSGKEPTWNFWKYLVAPDGKVVGAWDPTVSVEEVRPQITALVRKLILLKREDL

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FIGURE 121

CGGACGCGTGGGCGGGCCGGGACGCAGGGCAAAGCGAGCC<u>ATG</u>GCTGTCTACGTCGGGATGC TGCGCCTGGGGAGGCTGTGCGCCGGGAGCTCGGGGGTGCTGGGGGGCCCGGGCCCCTCTCT CGGAGTTGGCAGGAAGCCAGGTTGCAGGGTGTCCGCTTCCTCAGTTCCAGAGAGGTGGATCG CATGGTCTCCACGCCCATCGGAGGCCTCAGCTACGTTCAGGGGTGCACCAAAAAGCATCTTA ACAGCAAGACTGTGGGCCAGTGCCTGGAGACCACAGCACAGAGGGTCCCAGAACGAGAGGCC TTGGTCGTCCTCCATGAAGACGTCAGGTTGACCTTTGCCCAACTCAAGGAGGAGGTGGACAA AGCTGCTTCTGGCCTCCTGAGCATTGGCCTCTGCAAAGGTGACCGGCTGGGCATGTGGGGAC CTAACTCCTATGCATGGGTGCTCATGCAGTTGGCCACCGCCCAGGCGGGCATCATTCTGGTG TCTGTGAACCCAGCCTACCAGGCTATGGAACTGGAGTATGTCCTCAAGAAGGTGGGCTGCAA GGCCCTTGTGTTCCCCAAGCAATTCAAGACCCAGCAATACTACAACGTCCTGAAGCAGATCT GTCCAGAAGTGGAGAATGCCCAGCCAGGGGCCTTGAAGAGTCAGAGGCTCCCAGATCTGACC ACAGTCATCTCGGTGGATGCCCCTTTGCCGGGGACCCTGCTCCTGGATGAAGTGGTGGCGGC TGGCAGCACACGGCAGCATCTGGACCAGCTCCAATACAACCAGCAGTTCCTGTCCTGCCATG ACCCCATCAACATCCAGTTCACCTCGGGGACAACAGGCAGCCCCAAGGGGGCCACCCTCTCC CACTACAACATTGTCAACAACTCCAACATTTTAGGAGAGCGCCTGAAACTGCATGAGAAGAC ACCAGAGCAGTTGCGGATGATCCTGCCCAACCCCCTGTACCATTGCCTGGGTTCCGTGGCAG GCACAATGATGTCTGATGTACGGTGCCACCCTCATCCTGGCCTCTCCCATCTTCAATGGC AAGAAGGCACTGGAGGCCATCAGCAGAGAGAGAGGCACCTTCCTGTATGGTACCCCCACGAT GTTCGTGGACATTCTGAACCAGCCAGACTTCTCCAGTTATGACATCTCGACCATGTGTGGAG GTGTCATTGCTGGGTCCCCTGCACCTCCAGAGTTGATCCGAGCCATCATCAACAAGATAAAT ATGAAGGACCTGGTGGTTGCTTATGGAACCACAGAGAACAGTCCCGTGACATTCGCGCACTT CCCTGAGGACACTGTGGAGCAGAAGGCAGAAAGCGTGGGCAGAATTATGCCTCACACGGAGG CCCGGATCATGAACATGGAGGCAGGGACGCTGGCAAAGCTGAACACGCCCGGGGAGCTGTGC ATCCGAGGGTACTGCGTCATGCTGGGCTACTGGGGTGAGCCTCAGAAGACAGAGGAAGCAGT AGATCGTGGGCCGCTCTAAGGATATGATCATCCGGGGTGGTGAGAACATCTACCCCGCAGAG CTCGAGGACTTCTTTCACACACCCGAAGGTGCAGGAAGTGCAGGTGGTGGAGGTGAAGGA CGATCGGATGGGGGAAGAGTTTGTGCCTGCATTCGGCTGAAGGACGGGGGAGGACCACGG TGGAGGAGATAAAAGCTTTCTGCAAAGGGAAGATCTCTCACTTCAAGATTCCGAAGTACATC GTGTTTGTCACAAACTACCCCCTCACCATTTCAGGAAAGATCCAGAAATTCAAACTTCGAGA GCAGATGGAACGACATCTAAATCTG**TGA**ATAAAGCAGCAGGCCTGTCCTGGCCGGTTGGCTT GACTCTCTCCTGTCAGAATGCAACCTGGCTTTATGCACCTAGATGTCCCCAGCACCCAGTTC TCCATCCCCACATTCCCCTGTCTGTCCTTGTGATTTGGCATAAAGAGCTTCTGTTTTCTTT GAAAAAAAAAAAAAA

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FIGURE 122

MAVYVGMLRLGRLCAGSSGVLGARAALSRSWQEARLQGVRFLSSREVDRMVSTPIGGLSYVQ
GCTKKHLNSKTVGQCLETTAQRVPEREALVVLHEDVRLTFAQLKEEVDKAASGLLSIGLCKG
DRLGMWGPNSYAWVLMQLATAQAGIILVSVNPAYQAMELEYVLKKVGCKALVFPKQFKTQQY
YNVLKQICPEVENAQPGALKSQRLPDLTTVISVDAPLPGTLLLDEVVAAGSTRQHLDQLQYN
QQFLSCHDPINIQFTSGTTGSPKGATLSHYNIVNNSNILGERLKLHEKTPEQLRMILPNPLY
HCLGSVAGTMMCLMYGATLILASPIFNGKKALEAISRERGTFLYGTPTMFVDILNQPDFSSY
DISTMCGGVIAGSPAPPELIRAIINKINMKDLVVAYGTTENSPVTFAHFPEDTVEQKAESVG
RIMPHTEARIMNMEAGTLAKLNTPGELCIRGYCVMLGYWGEPQKTEEAVDQDKWYWTGDVAT
MNEQGFCKIVGRSKDMIIRGGENIYPAELEDFFHTHPKVQEVQVVGVKDDRMGEEICACIRL
KDGEETTVEEIKAFCKGKISHFKIPKYIVFVTNYPLTISGKIQKFKLREQMERHLNL

Signal Peptide:

amino acids 1-22

Transmembrane Domains:

amino acids 140-161, 213-229, 312-334

Putative AMP-binding Domain Signature:

amino acids 260-271

N-myristoylation Sites:

amino acids 19-24, 22-27, 120-125, 203-208, 268-273, 272-277, 314-319, 318-323, 379-384, 380-385, 409-413

N-glycosylation Site:

amino acids 282-285

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FIGURE 123

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FIGURE 124

GAGCAGGACGGAGCCATGGACCCCGCCAGGAAAGCAGGTGCCCAGGCCATGATCTGGACTGC AGGCTGCTGCTGCTGCTTCGCGGAGGAGCGCAGGCCCTGGAGTGCTACAGCTGCG TGCAGAAAGCAGATGACGGATGCTCCCCGAACAAGATGAAGACAGTGAAGTGCGCGCCGGGC GTGGACGTCTGCACCGAGGCCGTGGGGGCGGTGGAGACCATCCACGGACAATTCTCGCTGGC AGTGCGGGGTTGCGGTTCGGGACTCCCCGGCAAGAATGACCGCGGCCTGGATCTTCACGGGC TTCTGGCGTTCATCCAGCTGCAGCATGCGCTCAGGATCGCTGCAACGCCAAGCTCAACCTC ACCTCGCGGGCGCTCGACCCGGCAGGTAATGAGAGTGCATACCCGCCCAACGGCGTGGAGTG CTACAGCTGTGTGGGCCTGAGCCGGGAGGCGTGCCAGGGTACATCGCCGCCGGTCGTGAGCT GCTACAACGCCAGCGATCATGTCTACAAGGGCTGCTTCGACGGCAACGTCACCTTGACGGCA GCTAATGTGACTGTCCTTGCCTGTCCGGGGCTGTGTCCAGGATGAATTCTGCACTCGGGA TGGAGTAACAGGCCCAGGGTTCACGCTCAGTGGCTCCTGTTGCCAGGGGTCCCGCTGTAACT CTGACCTCGCAACAAGACCTACTTCTCCCCTCGAATCCCACCCCTTGTCCGGCTGCCCCCT CCAGAGCCCACGACTGTGGCCTCAACCACATCTGTCACCACTTCTACCTCGGCCCCAGTGAG ACCCACATCCACCACCAAACCCATGCCAGCGCCAACCAGTCAGACTCCGAGACAGGGAGTAG AACACGAGGCCTCCCGGGATGAGGAGCCCAGGTTGACTGGAGGCGCCGCTGGCCACCAGGAC CGCAGCAATTCAGGGCAGTATCCTGCAAAAGGGGGGCCCCAGCAGCCCCATAATAAAGGCTG TGTGGCTCCCACAGCTGGATTGGCAGCCCTTCTGTTGGCCGTGGCTGCTGGTGTCCTACTG<u>T</u> **GA**GCTTCTCCACCTGGAAATTTCCCTCTCACCTACTTCTCTGGCCCTGGGTACCCCTCTTCT CATCACTTCCTGTTCCCACCACTGGACTGGGCTGGCCCAGCCCCTGTTTTTCCAACATTCCC CAGTATCCCCAGCTTCTGCTGCGCTGGTTTGCGGCTTTTGGGAAATAAAATACCGTTGTATAT ATTCTGCCAGGGGTGTTCTAGCTTTTTGAGGACAGCTCCTGTATCCTTCTCATCCTTGTCTC TCCGCTTGTCCTCTTGTGATGTTAGGACAGAGTGAGAGAAGTCAGCTGTCACGGGGAAGGTG GGTGGGTGGGACAATGGCTCCCCACTCTAAGCACTGCCTCCCCTACTCCCGCATCTTTGGG GAATCGGTTCCCCATATGTCTTCCTTACTAGACTGTGAGCTCCTCGAGGGGGGGCCCGGTAC CCAATTCGCCCTATAGTGAGTCGTA

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FIGURE 125

MDPARKAGAQAMIWTAGWLLLLLRGGAQALECYSCVQKADDGCSPNKMKTVKCAPGVDVCT EAVGAVETIHGQFSLAVRGCGSGLPGKNDRGLDLHGLLAFIQLQQCAQDRCNAKLNLTSRAL DPAGNESAYPPNGVECYSCVGLSREACQGTSPPVVSCYNASDHVYKGCFDGNVTLTAANVTV SLPVRGCVQDEFCTRDGVTGPGFTLSGSCCQGSRCNSDLRNKTYFSPRIPPLVRLPPPEPTT VASTTSVTTSTSAPVRPTSTTKPMPAPTSQTPRQGVEHEASRDEEPRLTGGAAGHQDRSNSG QYPAKGGPQQPHNKGCVAPTAGLAALLLAVAAGVLL

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FIGURE 126

CGGGACTCGGCGGTCCTCCTGGGAGTCTCGGAGGGGACCGGCTGTGCAGACGCCATG TGGTGCTGGTCTTCCTCTGCAGCCTGCTGGCCCCCATGGTCCTGGCCAGTGCAGCTGAAAAG GAGAAGGAAATGGACCCTTTTCATTATGATTACCAGACCCTGAGGATTGGGGGACTGGTGTT CGCTGTGGTCCTCTTCTCGGTTGGGATCCTCCTTATCCTAAGTCGCAGGTGCAAGTGCAGTT TCAATCAGAAGCCCCGGGCCCCAGGAGATGAGGAAGCCCAGGTGGAGAACCTCATCACCGCC AATGCAACAGAGCCCCAGAAGCAGAGAACTGAAGTGCAGCCATCAGGTGGAAGCCTCTGGAA CCTGAGGCGGCTGCTTGAACCTTTGGATGCAAATGTCGATGCT**TAA**GAAAACCGGCCACTTC AGCAACAGCCCTTTCCCCAGGAGAAGCCAAGAACTTGTGTGTCCCCCCACCCTATCCCCTCTA ACACCATTCCTCCACCTGATGATGCAACTAACACTTGCCTCCCCACTGCAGCCTGCGGTCCT CCCAGGCAGGGGCTGAGCCACATGGCCATCTGCTCCTCCCTGCCCCCGTGGCCCTCCATCAC CTTCTGCTCCTAGGAGGCTGCTTGTTGCCCGAGACCAGCCCCCTCCCCTGATTTAGGGATGC GTAGGGTAAGAGCACGGGCAGTGGTCTTCAGTCGTCTTGGGACCTGGGAAGGTTTGCAGCAC TTTGTCATCATTCTTCATGGACTCCTTTCACTCCTTTAACAAAACCTTGCTTCCTTATCCC ACCTGATCCCAGTCTGAAGGTCTCTTAGCAACTGGAGATACAAAGCAAGGAGCTGGTGAGCC CAGCGTTGACGTCAGGCAGGCTATGCCCTTCCGTGGTTAATTTCTTCCCAGGGGGCTTCCACG AGGAGTCCCCATCTGCCCCGCCCTTCACAGAGCGCCCGGGGATTCCAGGCCCAGGGCTTCT ACTCTGCCCCTGGGGAATGTGTCCCCTGCATATCTTCTCAGCAATAACTCCATGGGCTCTGG GACCCTACCCCTTCCAACCTTCCCTGCTTCTGAGACTTCAATCTACAGCCCAGCTCATCCAG GTTGGGGCCAGCACCCGGGATGGATGGAGGGGAGAGCCGTTTGCTTCTCTGCCTACG TCCCCTTAGATGGGCAGCAGGCAACTCCCGCATCCTTTGCTCTGCCTGTCGGTGGTCAGA GCGGTGAGCGAGGTTGGAGACTCAGCAGGCTCCGTGCAGCCCTTGGGAACAGTGAGAG GTTGAAGGTCATAACGAGAGTGGGAACTCAACCCAGATCCCGCCCCTCCTGTCCTCTGTGTT CCCGCGGAAACCAACCAAACCGTGCGCTGTGACCCATTGCTGTTCTCTGTATCGTGATCTAT CCTCAACAACAACAGAAAAAAGGAATAAAATATCCTTTGTTTCCT

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FIGURE 127

MELVLVFLCSLLAPMVLASAAEKEKEMDPFHYDYQTLRIGGLVFAVVLFSVGILLILSRRCK CSFNQKPRAPGDEEAQVENLITANATEPQKQRTEVQPSGGSLWNLRRLLEPLDANVDA

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FIGURE 128

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FIGURE 129

MKIPVLPAVVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSAFKADE FLNWHALFESIKRKLPFLNWDAFPKLKGLRSATPDAQ

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FIGURE 130

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FIGURE 131

MGVEIAFASVILTCLSLLAAGVSQVVLLQPVPTQETGPKAMGDLSCGFAGHS

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FIGURE 132

GGGGAATCTGCAGTAGGTCTGCCGGCGATGGAGTGGTGGGCTAGCTCGCCGCTTCGGCTCTG GCTGCTGTTGTTCCTCCTGCCCTCAGCGCCAGGGGCCGCCAGAAGGAGTCAGGTTCAAAATGGA AAGTATTTATTGACCAAATTAACAGGTCTTTGGAGAATTACGAACCATGTTCAAGTCAAAAC TGCAGCTGCTACCATGGTGTCATAGAAGAGGATCTAACTCCTTTCCGAGGAGGCATCTCCAG GAAGATGATGGCAGAGGTAGTCAGACGGAAGCTAGGGACCCACTATCAGATCACTAAGAACA GACTGTACCGGGAAAATGACTGCATGTTCCCCTCAAGGTGTAGTGGTGTTGAGCACTTTATT TTGGAAGTGATCGGGCGTCTCCCTGACATGGAGATGGTGATCAATGTACGAGATTATCCTCA GGTTCCTAAATGGATGGAGCCTGCCATCCCAGTCTTCTCCTTCAGTAAGACATCAGAGTACC ATGATATCATGTATCCTGCTTGGACATTTTGGGAAGGGGGACCTGCTGTTTGGCCAATTTAT CCTACAGGTCTTGGACGGTGGGACCTCTTCAGAGAAGATCTGGTAAGGTCAGCAGCACAGTG GCCATGGAAAAAGAAAACTCTACAGCATATTTCCGAGGATCAAGGACAAGTCCAGAACGAG ATCCTCTCATTCTTCTCTCGGAAAAACCCAAAACTTGTTGATGCAGAATACACCAAAAAC CAGGCCTGGAAATCTATGAAAGATACCTTAGGAAAGCCAGCTGCTAAGGATGTCCATCTTGT GGATCACTGCAAATACAAGTATCTGTTTAATTTTCGAGGCGTAGCTGCAAGTTTCCGGTTTA AACACCTCTTCCTGTGTGGCTCACTTGTTTTCCATGTTGGTGATGAGTGGCTAGAATTCTTC TATCCACAGCTGAAGCCATGGGTTCACTATATCCCAGTCAAAACAGATCTCTCCAATGTCCA AGAGCTGTTACAATTTGTAAAAGCAAATGATGATGTAGCTCAAGAGATTGCTGAAAGGGGAA GCCAGTTTATTAGGAACCATTTGCAGATGGATGACATCACCTGTTACTGGGAGAACCTCTTG AGTGAATACTCTAAATTCCTGTCTTATAATGTAACGAGAAGGAAAGGTTATGATCAAATTAT TCCCAAAATGTTGAAAACTGAACTA**TAG**TAGTCATCATAGGACCATAGTCCTCTTTGTGGCA ACAGATCTCAGATATCCTACGGTGAGAAGCTTACCATAAGCTTGGCTCCTATACCTTGAATA TCTGCTATCAAGCCAAATACCTGGTTTTCCTTATCATGCTGCACCCAGAGCAACTCTTGAGA AAGATTTAAAATGTGTCTAATACACTGATATGAAGCAGTTCAACTTTTTGGATGAATAAGGA CCAGAAATCGTGAGATGTGGATTTTGAACCCAACTCTACCTTTCATTTTCTTAAGACCAATC ACAGCTTGTGCCTCAGATCATCCACCTGTGTGAGTCCATCACTGTGAAATTGACTGTGTCCA TGTGATGATGCCCTTTGTCCCATTATTTGGAGCAGAAAATTCGTCATTTGGAAGTAGTACAA CTCATTGCTGGAATTGTGAAATTATTCAAGGCGTGATCTCTGTCACTTTATTTTAATGTAGG AAACCCTATGGGGTTTATGAAAAATACTTGGGGATCATTCTCTGAATGGTCTAAGGAAGCGG TAGCCATGCCATGCAATGATGTAGGAGTTCTCTTTTGTAAAACCATAAACTCTGTTACTCAG GAGGTTTCTATAATGCCACATAGAAAGAGGCCAATTGCATGAGTAATTATTGCAATTGGATT TCAGGTTCCCTTTTTGTGCCTTCATGCCCTACTTCTTAATGCCTCTCTAAAGCCAAA

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FIGURE 133

MEWWASSPLRLWLLLFLLPSAQGRQKESGSKWKVFIDQINRSLENYEPCSSQNCSCYHGVIE EDLTPFRGGISRKMMAEVVRRKLGTHYQITKNRLYRENDCMFPSRCSGVEHFILEVIGRLPD MEMVINVRDYPQVPKWMEPAIPVFSFSKTSEYHDIMYPAWTFWEGGPAVWPIYPTGLGRWDL FREDLVRSAAQWPWKKKNSTAYFRGSRTSPERDPLILLSRKNPKLVDAEYTKNQAWKSMKDT LGKPAAKDVHLVDHCKYKYLFNFRGVAASFRFKHLFLCGSLVFHVGDEWLEFFYPQLKPWVH YIPVKTDLSNVQELLQFVKANDDVAQEIAERGSQFIRNHLQMDDITCYWENLLSEYSKFLSY NVTRRKGYDQIIPKMLKTEL

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FIGURE 134

CACCCTCCATTTCTCGCCATGCCCCTGCACTGCTCCTGATCCCTGCTGCCCTCGCCTCTT TCATCCTGGCCTTTGGCACCGGAGTGGAGTTCGTGCGCTTTACCTCCCTTCGGCCACTTCTT CCGCAGCATCCTTGCCCCCTGGCATGGGATCTGGGGCTCCTGCTTCTATTTGTTGGGCAGC ACAGCCTCATGGCAGCTGAAAGAGTGAAGGCATGGACATCCCGGTACTTTGGGGTCCTTCAG AGGTCACTGTATGTGGCCTGCACTGCCCTGGCCTTGCAGCTGGTGATGCGGTACTGGGAGCC CATACCCAAAGGCCCTGTGTTGTGGGAGGCTCGGGCTGAGCCATGGGCCACCTGGGTGCCGC TCCTCTGCTTTGTGCTCCATGTCATCTCCTGGCTCCTCATCTTTAGCATCCTTCTCGTCTTT GACTATGCTGAGCTCATGGGCCTCAAACAGGTATACTACCATGTGCTGGGGCTGGGCGAGCC TCTGGCCCTGAAGTCTCCCCGGGCTCTCAGACTCTTCTCCCACCTGCGCCACCCAGTGTGTG TGGAGCTGCTGACAGTGCTGTGGGTGGTGCCTACCCTGGGCACGGACCGTCTCCTCCTTGCT TTCCTCCTTACCTCTACCTGGGCCTGGCTCACGGGCTTGATCAGCAAGACCTCCGCTACCT CCGGGCCCAGCTACAAAGAAAACTCCACCTGCTCTCTCGGCCCCAGGATGGGGAGGCAGAGT **GA**GGAGCTCACTCTGGTTACAAGCCCTGTTCTTCCTCTCCCACTGAATTCTAAATCCTTAAC ATCCAGGCCCTGGCTGCTTCATGCCAGAGGCCCAAATCCATGGACTGAAGGAGATGCCCCTT CTACTACTTGAGACTTTATTCTCTGGGTCCAGCTCCATACCCTAAATTCTGAGTTTCAGCCA CTGAACTCCAAGGTCCACTTCTCACCAGCAAGGAAGAGTGGGGTATGGAAGTCATCTGTCCC TTCACTGTTTAGAGCATGACACTCTCCCCTCAACAGCCTCCTGAGAAGGAAAGGATCTGCC CTGACCACTCCCTGGCACTGTTACTTGCCTCTGCGCCTCAGGGGTCCCCTTCTGCACCGCT GGCTTCCACTCCAAGAAGGTGGACCAGGGTCTGCAAGTTCAACGGTCATAGCTGTCCCTCCA GGCCCCAACCTTGCCTCACCACTCCCGGCCCTAGTCTCTGCACCTCCTTAGGCCCTGCCTCT GGGCTCAGACCCAACCTAGTCAAGGGGATTCTCCTGCTCTTAACTCGATGACTTGGGGCTC

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FIGURE 135

MAPALLLIPAALASFILAFGTGVEFVRFTSLRPLLGGIPESGGPDARQGWLAALQDRSILAP LAWDLGLLLLFVGQHSLMAAERVKAWTSRYFGVLQRSLYVACTALALQLVMRYWEPIPKGPV LWEARAEPWATWVPLLCFVLHVISWLLIFSILLVFDYAELMGLKQVYYHVLGLGEPLALKSP RALRLFSHLRHPVCVELLTVLWVVPTLGTDRLLLAFLLTLYLGLAHGLDQQDLRYLRAQLQR KLHLLSRPQDGEAE

Signal sequence:

amino acids 1-13

Transmembrane domains:

amino acids 58-76, 99-113, 141-159, 203-222

N-myristoylation sites:

amino acids 37-43, 42-48, 229-235

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FIGURE 136

CCGAGCACAGGAGATTGCCTGCGTTTAGGAGGTGGCTGCGTTGTGGGAAAAGCTATCAAGGA AGAAATTGCCAAACCATGTCTTTTTTTCTGTTTTCAGAGTAGTTCACAACAGATCTGAGTGT TTTAATTAAGCATGGAATACAGAAAACAACAAAAAACTTAAGCTTTAATTTCATCTGGAATT TCACGTGGTGCTCTCCGACTACTCACCCCGAGTGTAAAGAACCTTCGGCTCGCGTGCTTCTG AGCTGCTGTGGATGCCTCGGCTCTCTGGACTGTCCTTCCGAGTAGGATGTCACTGAGATCC CTCAAATGGAGCCTCCTGCTGTCACTCCTGAGTTTCTTTGTGATGTGGTACCTCAGCCT TCCCCACTACAATGTGATAGAACGCGTGAACTGGATGTACTTCTATGAGTATGAGCCGATTT ACAGACAAGACTTTCACTTCACACTTCGAGAGCATTCAAACTGCTCTCATCAAAATCCATTT TTGGGGTGAAAAAAGTCTTGGTGGGGATATGAGGTTCTTACATTTTTCTTATTAGGCCAAG AGGCTGAAAAGGAAGACAAAATGTTGGCATTGTCCTTAGAGGATGAACACCTTCTTTATGGT GACATAATCCGACAAGATTTTTTAGACACATATAATAACCTGACCTTGAAAACCATTATGGC TTTTCATCAATACTGGCAATTTAGTGAAGTATCTTTTAAACCTAAACCACTCAGAGAAGTTT TTCACAGGTTATCCTCTAATTGATAATTATTCCTATAGAGGATTTTACCAAAAAACCCATAT TTCTTACCAGGAGTATCCTTTCAAGGTGTTCCCTCCATACTGCAGTGGGTTGGGTTATATAA TGTCCAGAGATTTGGTGCCAAGGATCTATGAAATGATGGGTCACGTAAAACCCATCAAGTTT GAAGATGTTTATGTCGGGATCTGTTTGAATTTATTAAAAGTGAACATTCATATTCCAGAAGA CAGCCCATGGCTTTTCTTCCAAGGAGATCATCACTTTTTGGCAGGTCATGCTAAGGAACACC ACATGCCATTAT**TAA**CTTCACATTCTACAAAAAGCCTAGAAGGACAGGATACCTTGTGGAAA GTGTTAAATAAAGTAGGTACTGTGGAAAATTCATGGGGAGGTCAGTGTGCTGGCTTACACTG AACTGAAACTCATGAAAAACCCAGACTGGAGGACTGGAGGGTTACACTTGTGATTTATTAGTC AGGCCCTTCAAAGATGATATGTGGAGGAATTAAATATAAAGGAATTGGAGGTTTTTGCTAAA GAAATTAATAGGACCAAACAATTTGGACATGTCATTCTGTAGACTAGAATTTCTTAAAAGGG AACAATGTAGTCACTTGAAGGTTTTGTGTATATCTTATGTGGATTACCAATTTAAAAATATA TGTAGTTCTGTGTCAAAAAACTTCTTCACTGAAGTTATACTGAACAAAATTTTACCTGTTTT TGGTCATTTATAAAGTACTTCAAGATGTTGCAGTATTTCACAGTTATTATTATTAAAATTA CTTCAACTTTGTGTTTTTAAATGTTTTGACGATTTCAATACAAGATAAAAAGGATAGTGAAT CATTCTTTACATGCAAACATTTTCCAGTTACTTAACTGATCAGTTTATTATTGATACATCAC TCCATTAATGTAAAGTCATAGGTCATTATTGCATATCAGTAATCTCTTGGACTTTGTTAAAT ATTTTACTGTGGTAATATAGAGAAGAATTAAAGCAAGAAAATCTGAAAA

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FIGURE 137

MASALWTVLPSRMSLRSLKWSLLLLSLLSFFVMWYLSLPHYNVIERVNWMYFYEYEPIYRQD FHFTLREHSNCSHQNPFLVILVTSHPSDVKARQAIRVTWGEKKSWWGYEVLTFFLLGQEAEK EDKMLALSLEDEHLLYGDIIRQDFLDTYNNLTLKTIMAFRWVTEFCPNAKYVMKTDTDVFIN TGNLVKYLLNLNHSEKFFTGYPLIDNYSYRGFYQKTHISYQEYPFKVFPPYCSGLGYIMSRD LVPRIYEMMGHVKPIKFEDVYVGICLNLLKVNIHIPEDTNLFFLYRIHLDVCQLRRVIAAHG FSSKEIITFWQVMLRNTTCHY

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FIGURE 138

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FIGURE 139

MKFTIVFAGLLGVFLAPALANYNINVNDDNNNAGSGQQSVSVNNEHNVANVDNNNGWDSWNS IWDYGNGFAATRLFQKKTCIVHKMNKEVMPSIQSLDALVKEKKLQGKGPGGPPPKGLMYSVN PNKVDDLSKFGKNIANMCRGIPTYMAEEMQEASLFFYSGTCYTTSVLWIVDISFCGDTVEN

Signal Peptide:

amino acids 1-20

N-myristoylation Sites:

amino acids 67-72, 118-123, 163-168

Flavodoxin protein homology:

amino acids 156-174

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FIGURE 140

CATTTCTGAAACTAATCGTGTCAGAATTGACTTTGAAAAGCATTGCTTTTTACAGAAGTATA TTAACTTTTTAGGAGTAATTTCTAGTTTGGATTGTAATATGAAATAATTTAAAAGGGCTTCG CTCATATATAGGAAAATCGCATATGGTCCTAGTATTAAATTCTTATTGCTTACTGATTTTTT TTGTTCGATTTCAACCAGAGACTATAGCATGTGCTTGCATCTACCTTGCAGCTAGAGCACTT CAGATTCCGTTGCCAACTCGTCCCCATTGGTTTCTTCTTTTTTGGTACTACAGAAGAGAAAAT CCAGGAAATCTGCATAGAAACACTTAGGCTTTATACCAGAAAAAAGCCAAACTATGAATTAC TGGAAAAAGAAGTAGAAAAAAGAAAGTAGCCTTACAAGAAGCCAAATTAAAAGCAAAGGGA TTGAATCCGGATGGAACTCCAGCCCTTTCAACCCTGGGTGGATTTTCTCCAGCCTCCAAGCC ATCATCACCAAGAGAAGTAAAAGCTGAAGAGAAATCACCAATCTCCATTAATGTGAAGACAG TCAAAAAGAACCTGAGGATAGACAACAGGCTTCCAAAAGCCCTTACAATGGTGTAAGAAAA TTCTAGATCACATACTCCAAGAAGACACTATAATAATAGGCGGAGTCGATCTGGAACATACA GCTCGAGATCAAGAAGCAGGTCCCGCAGTCACAGTGAAAGCCCTCGAAGACATCATAATCAT GGTTCTCCTCACCTTAAGGCCAAGCATACCAGAGATGATTTAAAAAGTTCAAACAGACATGG TCATAAAAGGAAAAATCTCGTTCTCGATCTCAGAGCAAGTCTCGGGATCACTCAGATGCAG CCAAGAAACACAGGCATGAAAGGGGACATCATAGGGACAGGCGTGAACGATCTCGCTCCTTT CTGACTTTCTCTTTGAGCCTGCATCAGTTCTTGGTTTTTGCCTATCTACAGTGTGATGT ATGGACTCAATCAAAAACATTAAACGCAAACTGATTAGGATTTGATTTCTTGAAACCCTCTA GGTCTCTAGAACACTGAGGACAGTTTCTTTTGAAAAGAACTATGTTAATTTTTTTGCACATT AAAATGCCCTAGCAGTATCTAATTAAAAACCATGGTCAGGTTCAATTGTACTTTATTATAGT TGTGTATTGTTTATTGCTATAAGAACTGGAGCGTGAATTCTGTAAAAATGTATCTTATTTTT ATACAGATAAAATTGCAGACACTGTTCTATTTAAGTGGTTATTTGTTTAAATGATGGTGAAT ACTTTCTTAACACTGGTTTGTCTGCATGTGTAAAGATTTTTACAAGGAAATAAAATACAAAT CTTGTTTTTCTAAAAAAAAAAAAAAAAAAGT

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FIGURE 141

MNDSLRTNVFVRFQPETIACACIYLAARALQIPLPTRPHWFLLFGTTEEEIQEICIETLRLY
TRKKPNYELLEKEVEKRKVALQEAKLKAKGLNPDGTPALSTLGGFSPASKPSSPREVKAEEK
SPISINVKTVKKEPEDRQQASKSPYNGVRKDSKRSRNSRSASRSRSRTRSRSRSHTPRRHYN
NRRSRSGTYSSRSRSRSRSHSESPRRHHNHGSPHLKAKHTRDDLKSSNRHGHKRKKSRSRSQ
SKSRDHSDAAKKHRHERGHHRDRRERSRSFERSHKSKHHGGSRSGHGRHRR

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FIGURE 142

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FIGURE 143

GGCACGAGGCCTCGTGCCAAGCTTGGCACGAGGGTGCACCGCGTTCTCGCACGCGTCATGGC GGTCCTCGGAGTACAGCTGGTGGTGACCCTGCTCACTGCCACCCTCATGCACAGGCTGGCGC CACACTGCTCCTTCGCGCGCTGCTGCTCTGTAACGGCAGTTTGTTCCGATACAAGCACCCG TCTGAGGAGGAGCTTCGGGCCCTGGCGGGGAAGCCGAGGCCCAGAGGCAGGAAAGAGCGGTG GGCCAATGGCCTTAGTGAGGAGAAGCCACTGTCTGTGCCCCGAGATGCCCCGTTCCAGCTGG AGACCTGCCCCTCACGACCGTGGATGCCCTGGTCCTGCGCTTCTTCCTGGAGTACCAGTGG TTTGTGGACTTTGCTGTGTACTCGGGCGGCGTGTACCTCTTCACAGAGGCCTACTACTACAT GCTGGGACCAGCCAAGGAGACTAACATTGCTGTGTTCTGGTGCCTGCTCACGGTGACCTTCT CCATCAAGATGTTCCTGACAGTGACACGGCTGTACTTCAGCGCCGAGGAGGGGGGTGAGCGC TCTGTCTGCCTCACCTTTGCCTTCCTCCTGCTGCCATGCTGGTGCAAGTGGTGCG GGAGGAGACCCTCGAGCTGGGCCTGGAGCCTGGTCTGGCCAGCATGACCCAGAACTTAGAGC CACTTCTGAAGAAGCAGGGCTGGGACTGGGCGCTTCCTGTGGCCAAGCTGGCTATCCGCGTG GGACTGGCAGTGGTGGCTCTGTGCTGGGTGCCTTCCTCACCTTCCCAGGCCTGCGGCTGGC CCAGACCCACCGGGACGCACTGACCATGTCGGAGGACAGACCCATGCTGCAGTTCCTCCTGC ACACCAGCTTCCTGTCTCCCCTGTTCATCCTGTGGCTCTGGACAAAGCCCATTGCACGGGAC TTCCTGCACCAGCCGCCGTTTGGGGAGACGCGTTTCTCCCTGCTGTCCGATTCTGCCTTCGA CTCTGGGCGCCTCTGGTTGCTGGTGCTGCCTGCCGGCTGGCGGTGACCCGGCCCC ACCTGCAGGCCTACCTGTGCCTGGCCAAGGCCCGGGTGGAGCAGCTGCGAAGGGAGGCTGGC CGCATCGAAGCCCGTGAAATCCAGCAGAGGGTGGTCCGAGTCTACTGCTATGTGACCGTGGT GAGCTTGCAGTACCTGACGCCGCTCATCCTCACCCTCAACTGCACACTTCTGCTCAAGACGC TGGGAGGCTATTCCTGGGGCCTGGGCCCAGCTCCTCTACTATCCCCCGACCCATCCTCAGCC AGCGCTGCCCCATCGGCTCTGGGGAGGACGAAGTCCAGCAGACTGCAGCGCGGATTGCCGG GGCCCTGGGTGGCCTGCTTACTCCCCTCTTCCTCCGTGGCGTCCTGGCCTACCTCATCTGGT GGACGCTGCCTGCCAGCTCTCGCCAGCCTTTTCGGCCTCTACTTCCACCAGCACTTGGCA GGCTCCTAGCTGCCTGCAGACCCTCCTGGGGCCCTGAGGTCTGTTCCTGGGGCAGCGGGACA CTAGCCTGCCCCTCTGTTTGCGCCCCCGTGTCCCCAGCTGCAAGGTGGGGCCGGACTCCCC GGCGTTCCCTTCACCACAGTGCCTGACCCGCGCCCCCTTGGACGCCGAGTTTCTGCCTCA GAACTGTCTCTCTGGGCCCAGCAGCATGAGGGTCCCGAGGCCATTGTCTCCGAAGCGTATG TGCCAGGTTTGAGTGGCGAGGGTGATGCTGGCTGCTCTTCTGAACAATAAAGGAGCATGCC **GATTTTTAA**

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FIGURE 144

MAVLGVQLVVTLLTATLMHRLAPHCSFARWLLCNGSLFRYKHPSEEELRALAGKPRPRGRKE
RWANGLSEEKPLSVPRDAPFQLETCPLTTVDALVLRFFLEYQWFVDFAVYSGGVYLFTEAYY
YMLGPAKETNIAVFWCLLTVTFSIKMFLTVTRLYFSAEEGGERSVCLTFAFLFLLLAMLVQV
VREETLELGLEPGLASMTQNLEPLLKKQGWDWALPVAKLAIRVGLAVVGSVLGAFLTFPGLR
LAQTHRDALTMSEDRPMLQFLLHTSFLSPLFILWLWTKPIARDFLHQPPFGETRFSLLSDSA
FDSGRLWLLVVLCLLRLAVTRPHLQAYLCLAKARVEQLRREAGRIEAREIQQRVVRVYCYVT
VVSLQYLTPLILTLNCTLLLKTLGGYSWGLGPAPLLSPDPSSASAAPIGSGEDEVQQTAARI
AGALGGLLTPLFLRGVLAYLIWWTAACQLLASLFGLYFHQHLAGS

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FIGURE 145

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FIGURE 146

GGTTCCTACATCCTCATCTGAGAATCAGAGAGCATAATCTTCTTACGGGCCCGTGATTTATTAACGTGGCTT AATCTGAAGGTTCTCAGTCAAATTCTTTGTGATCTACTGATTGTGGGGGCATGGCAAGGTTTGCTTAAAGGAGC $\tt TTGGCTGGTTTGGGCCCTTGTAGCTGACAGAAGGTGGCCAGGGAGAATGCAGCACACTGCTCGGAGA\underline{\textbf{ATG}}\textbf{AAGG}$ CGCTTCTGTTGCTGGTCTTGCCTTGGCTCAGTCCTGCTAACTACATTGACAATGTGGGCAACCTGCACTTCCTG TATTCAGAACTCTGTAAAGGTGCCTCCCACTACGGCCTGACCAAAGATAGGAAGAGGCGCTCACAAGATGGCTG TCCAGACGGCTGTGCGAGCCTCACAGCCACGGCTCCCCCAGAGGTTTCTGCAGCTGCCACCATCTCCTTAA GTGGACTCTGGCCGGAGCAACCGAACTAGGGCACGGCCCTTTGAGAGGATCCACTATTAGAAGCAGATCATTTAA AAAAATAAATCGAGCTTTGAGTGTTCTTCGAAGGACAAAGAGCGGGAGTGCAGTTGCCAACCATGCCGACCAGG GCAGGGAAAATTCTGAAAACACCACTGCCCCTGAAGTCTTTCCAAGGTTGTACCACCTGATTCCAGATGGTGAA ATTACCAGCATCAAGATCAATCGAGTAGATCCCAGTGAAAGCCTCTCTATTAGGCTGGTGGGAGGTAGCGAAAC GAGACATCATTCTAAAGGTCAACGGGATGGACATCAGCAATGTCCCTCACAACTACGCTGTGCGTCTCCTGCGG CAGCCCTGCCAGGTGCTGTGGCTGACTGTGATGCGTGAACAGAAGTTCCGCAGCAGGAACAATGGACAGGCCCC GGATGCCTACAGACCCCGAGATGACAGCTTTCATGTGATTCTCAACAAAAGTAGCCCCGAGGAGCAGCTTGGAA TAAAACTGGTGCGCAAGGTGGATGAGCCTGGGGTTTTCATCTTCAATGTGCTGGATGGCGGTGTGGCATATCGA CATGGTCAGCTTGAGGAGAATGACCGTGTGTTAGCCATCAATGGACATGATCTTCGATATGGCAGCCCAGAAAG TGCGGCTCATCTGATTCAGGCCAGTGAAAGACGTGTTCACCTCGTCGTGTCCCGCCAGGTTCGGCAGCGGAGCC CTGACATCTTTCAGGAAGCCGGCTGGAACAGCAATGGCAGCTGGTCCCCAGGGCCAGGGGAGAGCAACACT CCCAAGCCCCTCCATCCTACAATTACTTGTCATGAGAAGGTGGTAAATATCCAAAAAGACCCCGGTGAATCTCT GAGGAGTCATAAGCAGAGATGGAAGAATAAAAACAGGTGACATTTTGTTGAATGTGGATGGGGTCGAACTGACA GAGGTCAGCCGGAGTGAGCAGTGGCATTATTGAAAAGAACATCATCCTCGATAGTACTCAAAGCTTTGGAAGT GTGACTGGTCCCCATCCTGGGTCATGTGGCTGGAATTACCACGGTGCTTGTATAACTGTAAAAGATATTGTATTA TTTCATCAAATCCATTGTTGAAGGAACACCAGCATACAATGATGGAAGAATTAGATGTGGTGATATTCTTCTTG ATTACTCTAACTATTGTTTCTTGGCCTGGCACTTTTTTATATAGAATCAATGATGGGTCAGAGGAAAACAGAAAAA AAAAATGTCAGGAAAAGTATGATCATCTAATGAAAGCCAGTTACACCTCAGAAAATATGATTCCAAAAAAATTA AAACTACTAGTTTTTTTCAGTGTGGAGGATTTCTCATTACTCTACAACATTGTTTATATTTTTTCTATTCAAT AAAAAGCCCTAAAACAACTAAAATGATTGATTTGTATACCCCACTGAATTCAAGCTGATTTAAAATTTAAAATTT GGTATATGCTGAAGTCTGCCAAGGGTACATTATGGCCATTTTTAATTTACAGCTAAAATATTTTTTAAAATGCA TTGCTGAGAAACGTTGCTTTCATCAAACAAGAATAAATATTTTTCAGAAGTTAAA

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FIGURE 147

MKALLLLVLPWLSPANYIDNVGNLHFLYSELCKGASHYGLTKDRKRRSQDGCPDGCASLTAT
APSPEVSAAATISLMTDEPGLDNPAYVSSAEDGQPAISPVDSGRSNRTRARPFERSTIRSRS
FKKINRALSVLRRTKSGSAVANHADQGRENSENTTAPEVFPRLYHLIPDGEITSIKINRVDP
SESLSIRLVGGSETPLVHIIIQHIYRDGVIARDGRLLPGDIILKVNGMDISNVPHNYAVRLL
RQPCQVLWLTVMREQKFRSRNNGQAPDAYRPRDDSFHVILNKSSPEEQLGIKLVRKVDEPGV
FIFNVLDGGVAYRHGQLEENDRVLAINGHDLRYGSPESAAHLIQASERRVHLVVSRQVRQRS
PDIFQEAGWNSNGSWSPGPGERSNTPKPLHPTITCHEKVVNIQKDPGESLGMTVAGGASHRE
WDLPIYVISVEPGGVISRDGRIKTGDILLNVDGVELTEVSRSEAVALLKRTSSSIVLKALEV
KEYEPQEDCSSPAALDSNHNMAPPSDWSPSWVMWLELPRCLYNCKDIVLRNTAGSLGFCIV
GGYEEYNGNKPFFIKSIVEGTPAYNDGRIRCGDILLAVNGRSTSGMIHACLARLLKELKGRI
TLTIVSWPGTFL

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FIGURE 148

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FIGURE 149

MKILVAFLVVLTIFGIQSHGYEVFNIISPSNNGGNVQETVTIDNEKNTAIVNIHAGSCSSTT IFDYKHGYIASRVLSRRACFILKMDHQNIPPLNNLQWYIYEKQALDNMFSNKYTWVKYNPLE SLIKDVDWFLLGSPIEKLCKHIPLYKGEVVENTHNVGAGGCAKAGLLGILGISICADIHV

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FIGURE 150

ATGGGGCTCCCTGGGCTGTTCTGCTTGGCCGTGCTGCCAGCAGCTTCTCCAAGGCACG GGAGGAAGAATTACCCCTGTGGTCTCCATTGCCTACAAAGTCCTGGAAGTTTTCCCCAAAG GCCGCTGGGTGCTCATAACCTGCTGTGCACCCCAGCCACCACCGCCCATCACCTATTCCCTC TGTGGAACCAAGAACATCAAGGTGGCCAAGAAGGTGGTGAAGACCCACGAGCCGGCCTCCTT CAACCTCAACGTCACACTCAAGTCCAGTCCAGACCTGCTCACCTACTTCTGCCGGGCGTCCT CCACCTCAGGTGCCCATGTGGACAGTGCCAGGCTACAGATGCACTGGGAGCTGTGGTCCAAG CCAGTGTCTGAGCTGCGGGCCAACTTCACTCTGCAGGACAGAGGGGCAGGCCCCAGGGTGGA GATGATCTGCCAGGCGTCCTCGGGCAGCCCACCTATCACCAACAGCCTGATCGGGAAGGATG AGCCAGACATCGGACTGGTTCTGGTGCCAGGCTGCAAACAACGCCAATGTCCAGCACAGCGC CCTCACAGTGGTGCCCCCAGGTGGTGACCAGAAGATGGAGGACTGGCAGGGTCCCCTGGAGA GCCCCATCCTTGCCGCTCTACAGGAGCACCCGCCGTCTGAGTGAAGAGGAGTTTGGG GGGTTCAGGATAGGGAATGGGGAGGTCAGAGGACGCAAAGCAGCCATG**TAG**AATGAACC GTCCAGAGAGCCAAGCACGGCAGAGGACTGCAGGCCATCAGCGTGCACTGTTCGTATTTGGA

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FIGURE 151

MGLPGLFCLAVLAASSFSKAREEEITPVVSIAYKVLEVFPKGRWVLITCCAPQPPPPITYSL CGTKNIKVAKKVVKTHEPASFNLNVTLKSSPDLLTYFCRASSTSGAHVDSARLQMHWELWSK PVSELRANFTLQDRGAGPRVEMICQASSGSPPITNSLIGKDGQVHLQQRPCHRQPANFSFLP SQTSDWFWCQAANNANVQHSALTVVPPGGDQKMEDWQGPLESPILALPLYRSTRRLSEEEFG GFRIGNGEVRGRKAAAM

Signal Peptide:

amino acids 1-18

N-glycosylation Sites:

amino acids 86-89, 132-135, 181-184

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FIGURE 152

GGTCCTTAATCGCAGCAGCCGCCGCTACCAAGATCCTTCTGTGCCTCCCGCTTCTGCTCCTG CTGTCCGGCTGGTCCCGGCCTGGCCGACCCTCACTCTCTTTGCTATGACATCACCGT CATCCCTAAGTTCAGACCTGGACCACGGTGGTGTGCGGTTCAAGGCCAGGTGGATGAAAAGA CTTTTCTTCACTATGACTGTGGCAACAAGACAGTCACCTGTCAGTCCCCTGGGGAAGAAA CTAAATGTCACAACGGCCTGGAAAGCACAGAACCCAGTACTGAGAGAGGTGGTGGACATACT TACAGAGCAACTGCGTGACATTCAGCTGGAGAATTACACACCCAAGGAACCCCTCACCCTGC AGGCAAGGATGTCTTGTGAGCAGAAAGCTGAAGGACACAGCAGTGGATCTTGGCAGTTCAGT TTCGATGGGCAGATCTTCCTCCTCTTTGACTCAGAGAAGAGAATGTGGACAACGGTTCATCC TGGAGCCAGAAAGATGAAAGAAAAGTGGGAGAATGACAAGGTTGTGGCCATGTCCTTCCATT ACTTCTCAATGGGAGACTGTATAGGATGGCTTGAGGACTTCTTGATGGGCATGGACAGCACC CTGGAGCCAAGTGCAGGAGCACCACTCGCCATGTCCTCAGGCACAACCCAACTCAGGGCCAC AGCCACCACCCTCATCCTTTGCTGCCTCCTCATCATCCTCCCCTGCTTCATCCTCCCTGGCA TCTGAGGAGAGTCCTTTAGAGTGACAGGTTAAAGCTGATACCAAAAGGCTCCTGTGAGCACG GTCTTGATCAAACTCGCCCTTCTGTCTGGCCAGGCTGCCCACGACCTACGGTGTATGTCCAGT GGCCTCCAGCAGATCATGACATCATGGACCCAATAGCTCATTCACTGCCTTGATTCCTT TTGCCAACAATTTTACCAGCAGTTATACCTAACATATTATGCAATTTTCTCTTGGTGCTACC GTCAGTAAAATAATCACGTTAGACTTCAGACCTCTGGGGATTCTTTCCGTGTCCTGAAAGAG AATTTTTAAATTATTAATAAGAAAAATTTATATTAATGATTGTTTCCTTTAGTAATTTAT

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FIGURE 153

MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRWCAVQGQVDEKTFL HYDCGNKTVTPVSPLGKKLNVTTAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLTLQAR MSCEQKAEGHSSGSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAMSFHYFS MGDCIGWLEDFLMGMDSTLEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPCFILPGI

Important features:

Signal peptide:

amino acids 1-25

Transmembrane domain:

amino acids 224-246

N-glycosylation site.

amino acids 68-72, 82-86

N-myristoylation site.

amino acids 200-206, 210-216

Amidation site.

amino acids 77-81

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FIGURE 154

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FIGURE 155

MELIPTITSWRVLILVVALTQFWCGFLCRGFHLQNHELWLLIKREFGFYSKSQYRTWQKKLA EDSTWPPINRTDYSGDGKNGFYINGGYESHEQIPKRKLKLGGQPTEQHFWARL

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FIGURE 156

GTTCTCCTTTCCGAGCCAAAATCCCAGGCGATGGTGAATTATGAACGTGCCACACCATGAAG CTCTTGTGGCAGGTAACTGTGCACCACCACACCTGGAATGCCATCCTGCTCCCGTTCGTCTA CCTCACGGCGCAAGTGTGGATTCTGTGTGCAGCCATCGCTGCCGCCTCAGCCGGGCCCC AGAACTGCCCCTCCGTTTGCTCGTGCAGTAACCAGTTCAGCAAGGTGGTGTGCACGCGCCGG GGCCTCTCCGAGGTCCCGCAGGGTATTCCCTCGAACACCCGGTACCTCAACCTCATGGAGAA CAACATCCAGATGATCCAGGCCGACACCTTCCGCCACCTCCACCACCTGGAGGTCCTGCAGT TGGGCAGGAACTCCATCCGGCAGATTGAGGTGGGGGCCTTCAACGGCCTGGCCAGCCTCAAC ACCCTGGAGCTGTTCGACAACTGGCTGACAGTCATCCCTAGCGGGGCCTTTGAATACCTGTC CAAGCTGCGGGAGCTCTGGCTTCGCAACAACCCCATCGAAAGCATCCCCTCTTACGCCTTCA ACCGGGTGCCCTCCTCATGCGCCTGGACTTGGGGGAGCTCAAGAAGCTGGAGTATATCTCT GAGGGAGCTTTTGAGGGGCTGTTCAACCTCAAGTATCTGAACTTGGGCATGTGCAACATTAA AGACATGCCCAATCTCACCCCCCTGGTGGGGGTGGAGGAGCTGGAGATGTCAGGGAACCACT TCCCTGAGATCAGGCCTGGCTCCTTCCATGGCCTGAGCTCCCTCAAGAAGCTCTGGGTCATG CAACTTGGCCCACAATAACCTCTTCTTTGCCCCATGACCTCTTTACCCCGCTGAGGTACC TGGTGGAGTTGCATCTACACCACAACCCTTGGAACTGTGATTGTGACATTCTGTGGCTAGCC TGGTGGCTTCGAGAGTATATACCCACCAATTCCACCTGCTGTGGCCGCTGTCATGCTCCCAT GCACATGCGAGGCCGCTACCTCGTGGAGGTGGACCAGGCCTCCTTCCAGTGCTCTGCCCCCT TCATCATGGACGCACCTCGAGACCTCAACATTTCTGAGGGTCGGATGGCAGAACTTAAGTGT CGGACTCCCCTATGTCCTCCGTGAAGTGGTTGCTGCCCAATGGGACAGTGCTCAGCCACGC CTCCCGCCACCAAGGATCTCTGTCCTCAACGACGGCACCTTGAACTTTTCCCACGTGCTGC TTTCAGACACTGGGGTGTACACATGCATGGTGACCAATGTTGCAGGCAACTCCAACGCCTCG GCCTACCTCAATGTGAGCACGGCTGAGCTTAACACCTCCAACTACAGCTTCTTCACCACAGT AACAGTGGAGACCACGGAGATCTCGCCTGAGGACACAACGCGAAAGTACAAGCCTGTTCCTA CCACGTCCACTGGTTACCAGCCGGCATATACCACCTCTACCACGGTGCTCATTCAGACTACC CGTGTGCCCAAGCAGGTGCCAGTACCCGCGACAGACACCACTGACAAGATGCAGACCAGCCT GGATGAAGTCATGAAGACCACCAAGATCATCATTGGCTGCTTTGTGGCAGTGACTCTGCTAG CTGCCGCCATGTTGATTGTCTTCTATAAACTTCGTAAGCGGCACCAGCAGCGGAGTACAGTC ACAGCCGCCCGGACTGTTGAGATAATCCAGGTGGACGAAGACATCCCAGCAGCAACATCCGC AGCAGCAACAGCAGCTCCGTCCGGTGTATCAGGTGAGGGGGCAGTAGTGCTGCCCACAATTC ATGACCATATTAACTACAACACCTACAAACCAGCACATGGGGCCCACTGGACAGAAAACAGC CTGGGGAACTCTCTGCACCCCACAGTCACCACTATCTCTGAACCTTATATAATTCAGACCCA TACCAAGGACAAGGTACAGGAAACTCAAATA<u>TGA</u>CTCCCCTCCCCCAAAAAACTTATAAAAT GCAATAGAATGCACACAAAGACAGCAACTTTTGTACAGAGTGGGGAGAGACTTTTTCTTGTA CAAAAAGTCAAAACA

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FIGURE 157

MKLLWQVTVHHHTWNAILLPFVYLTAQVWILCAAIAAAASAGPQNCPSVCSCSNQFSKVVCT
RRGLSEVPQGIPSNTRYLNLMENNIQMIQADTFRHLHHLEVLQLGRNSIRQIEVGAFNGLAS
LNTLELFDNWLTVIPSGAFEYLSKLRELWLRNNPIESIPSYAFNRVPSLMRLDLGELKKLEY
ISEGAFEGLFNLKYLNLGMCNIKDMPNLTPLVGLEELEMSGNHFPEIRPGSFHGLSSLKKLW
VMNSQVSLIERNAFDGLASLVELNLAHNNLSSLPHDLFTPLRYLVELHLHHNPWNCDCDILW
LAWWLREYIPTNSTCCGRCHAPMHMRGRYLVEVDQASFQCSAPFIMDAPRDLNISEGRMAEL
KCRTPPMSSVKWLLPNGTVLSHASRHPRISVLNDGTLNFSHVLLSDTGVYTCMVTNVAGNSN
ASAYLNVSTAELNTSNYSFFTTVTVETTEISPEDTTRKYKPVPTTSTGYQPAYTTSTTVLIQ
TTRVPKQVAVPATDTTDKMQTSLDEVMKTTKIIIGCFVAVTLLAAAMLIVFYKLRKRHQQRS
TVTAARTVEIIQVDEDIPAATSAAATAAPSGVSGEGAVVLPTIHDHINYNTYKPAHGAHWTE
NSLGNSLHPTVTTISEPYIIQTHTKDKVQETQI

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FIGURE 158

CGCTCGGCACCAGCCGCGCAAGGATGGACTGGGTTGCTGGACGCAGTTGGGGCTCACTTTTCTTCAGCTCC TTCTCATCTCGTCCTTGCCAAGAGAGTACACAGTCATTAATGAAGCCTGCCCTGGAGCAGAGTGGAATATCATG TGTCGGGAGTGCTGTGAATATGATCAGATTGAGTGCGTCTGCCCCGGAAAGAGGGAAGTCGTGGGTTATACCAT GCAAGAGCTGCCGAAATGGCTCATGGGGGGGTACCTTGGATGACTTCTATGTGAAGGGGTTCTACTGTGCAGAG TGCCGAGCAGGCTGGTACGGAGGAGACTGCATGCGATGTGGCCAGGTTCTGCGAGCCCCAAAGGGTCAGATTTT GTTGGAAAGCTATCCCCTAAATGCTCACTGTGAATGGACCATTCATGCTAAACCTGGGTTTGTCATCCAACTAA GATTTGTCATGTTGAGTCTGGAGTTTGACTACATGTGCCAGTATGACTATGTTGAGGTTCGTGATGGAGACAAC CGCGATGGCCAGATCATCAAGCGTGTCTGTGGCAACGAGCGCCAGCTCCTATCCAGAGCATAGGATCCTCACT CCACGTCCTCTCCACTCCGATGGCTCCAAGAATTTTGACGGTTTCCATGCCATTTATGAGGAGATCACAGCAT GCTCCTCATCCCCTTGTTTCCATGACGGCACGTGCGTCCTTGACAAGGCTGGATCTTACAAGTGTGCCTGCTTG TGGGTACCAGAAAATAACAGGGGGCCCTGGGCTTATCAACGGACGCCATGCTAAAATTGGCACCGTGGTGTCTT TCTTTTGTAACAACTCCTATGTTCTTAGTGGCAATGAGAAAAGAACTTGCCAGCAGAATGGAGAGTGGTCAGGG AAACAGCCCATCTGCATAAAAGCCTGCCGAGAACCAAAGATTTCAGACCTGGTGAGAAGGAGAGTTCTTCCGAT CCCCTACCAAGAAGCCAGCCCTTCCCTTTGGAGATCTGCCCATGGGATACCAACATCTGCATACCCAGCTCCAG TATGAGTGCATCTCACCCTTCTACCGCCGCCTGGGCAGCAGCAGGACATGTCTGAGGACTGGGAAGTGGAG TGGGCGGCCCCTCCTGCATCCCTATCTGCGGGAAAATTGAGAACATCACTGCTCCAAAGACCCAAGGGTTGC GCTGGCCGTGGCAGCCATCTACAGGAGGACCAGCGGGGTGCATGACGGCAGCCTACACAAGGGAGCGTGG TTCCTAGTCTGCAGCGGTGCCCTGGTGAATGAGCGCACTGTGGTGGTGGCTGCCCACTGTGTTACTGACCTGGG GAAGGTCACCATGATCAAGACAGCCAGACCTGAAAGTTGTTTTGGGGAAATTCTACCGGGATGATGACCGGGATG AGAAGACCATCCAGAGCCTACAGATTTCTGCTATCATTCTGCATCCCAACTATGACCCCATCCTGCTTGATGCT GCCCTGGCTTCAAGAACGACACACTGCGCTCTGGGGTGGTCAGTGTGGTGGACTCGCTGCTGTGTGAGGAGCAG CATGAGGACCATGGCATCCCAGTGAGTGTCACTGATAACATGTTCTGTGCCAGCTGGGAACCCACTGCCCCTTC TGATATCTGCACTGCAGAGACAGGAGGCATCGCGGCTGTGTCCTTCCCGGGACGAGCATCTCCTGAGCCACGCT GGCATCTGATGGGACTGGTCAGCTGGAGCTATGATAAAACATGCAGCCACAGGCTCTCCACTGCCTTCACCAAG GTGCTGCCTTTTAAAGACTGGATTGAAAGAAATATGAAA<u>TGA</u>ACCATGCTCATGCACTCCTTGAGAAGTGTTTC TGTATATCCGTCTGTACGTGTGTCATTGCGTGAAGCAGTGTGGGCCTGAAGTGTGATTTGGCCTGTGAACTTGG CTGTGCCAGGGCTTCTGACTTCAGGGACAAAACTCAGTGAAGGGTGAGTAGACCTCCATTGCTGGTAGGCTGAT ATATACAAAACCTCTCCACTCCACTGACCTGGTGGTCTTCCCCAACTTTCAGTTATACGAATGCCATCAGCTTG ACCAGGGAAGATCTGGGCTTCATGAGGCCCCTTTTGAGGCTCTCAAGTTCTAGAGAGCTGCCTGTGGGACAGCC ΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑ

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FIGURE 159

MELGCWTQLGLTFLQLLLISSLPREYTVINEACPGAEWNIMCRECCEYDQIECVCPGKREVV
GYTIPCCRNEENECDSCLIHPGCTIFENCKSCRNGSWGGTLDDFYVKGFYCAECRAGWYGGD
CMRCGQVLRAPKGQILLESYPLNAHCEWTIHAKPGFVIQLRFVMLSLEFDYMCQYDYVEVRD
GDNRDGQIIKRVCGNERPAPIQSIGSSLHVLFHSDGSKNFDGFHAIYEEITACSSSPCFHDG
TCVLDKAGSYKCACLAGYTGQRCENLLEERNCSDPGGPVNGYQKITGGPGLINGRHAKIGTV
VSFFCNNSYVLSGNEKRTCQQNGEWSGKQPICIKACREPKISDLVRRRVLPMQVQSRETPLH
QLYSAAFSKQKLQSAPTKKPALPFGDLPMGYQHLHTQLQYECISPFYRRLGSSRRTCLRTGK
WSGRAPSCIPICGKIENITAPKTQGLRWPWQAAIYRRTSGVHDGSLHKGAWFLVCSGALVNE
RTVVVAAHCVTDLGKVTMIKTADLKVVLGKFYRDDDRDEKTIQSLQISAIILHPNYDPILLD
ADIAILKLLDKARISTRVQPICLAASRDLSTSFQESHITVAGWNVLADVRSPGFKNDTLRSG
VVSVVDSLLCEEQHEDHGIPVSVTDNMFCASWEPTAPSDICTAETGGIAAVSFPGRASPEPR
WHLMGLVSWSYDKTCSHRLSTAFTKVLPFKDWIERNMK

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FIGURE 160

ACCAGGCATTGTATCTTCAGTTGTCATCAAGTTCGCAATCAGATTGGAAAAGCTCAACTTGA AGCTTTCTTGCCTGCAGTGAAGCAGAGAGATAGATATTATTCACGTAATAAAAAAACATCGGC TTCAACCTGACTTTCCACCTTTCCTACAAATTCCGATTACTGTTGCTGTTGACTTTGTGCCT GACAGTGGTTGGGTGGCCACCAGTAACTACTTCGTGGGTGCCATTCAAGAGATTCCTAAAG CAAAGGAGTTCATGGCTAATTTCCATAAGACCCTCATTTTGGGGAAAGGGAAAAACTCTGACT AATGAAGCATCCACGAAGAAGGTAGAACTTGACAACTGTCCTTCTGTGTCTCCTTACCTCAG AGGCCAGAGCAAGCTCATTTTCAAACCAGATCTCACTTTGGAAGAGGTACAGGCAGAAAATC CCAAAGTGTCCAGAGGCCGGTATCGCCCTCAGGAATGTAAAGCTTTACAGAGGGTCGCCATC CTCGTTCCCCACCGGAACAGAGAGAAACACCTGATGTACCTGCTGGAACATCTGCATCCCTT CCTGCAGAGGCAGCAGCTGGATTATGGCATCTACGTCATCCACCAGGCTGAAGGTAAAAAGT TTAATCGAGCCAAACTCTTGAATGTGGGCTATCTAGAAGCCCTCAAGGAAGAAAATTGGGAC TGCTTTATATTCCACGATGTGGACCTGGTACCCGAGAATGACTTTAACCTTTACAAGTGTGA GGAGCATCCCAAGCATCTGGTGGTTGGCAGGAACAGCACTGGGTACAGGTTACGTTACAGTG GATATTTTGGGGGTGTTACTGCCCTAAGCAGAGAGCAGTTTTTCAAGGTGAATGGATTCTCT AACAACTACTGGGGATGGGGAGGCGAAGACGATGACCTCAGACTCAGGGTTGAGCTCCAAAG AATGAAAATTTCCCGGCCCCTGCCTGAAGTGGGTAAATATACAATGGTCTTCCACACTAGAG ACAAAGGCAATGAGGTGAACGCAGAACGGATGAAGCTCTTACACCAAGTGTCACGAGTCTGG AGAACAGATGGGTTGAGTAGTTGTTCTTATAAATTAGTATCTGTGGAACACAATCCTTTATA TATCAACATCACAGTGGATTTCTGGTTTGGTGCATGACCCTGGATCTTTTGGTGATGTTTGG AAGAACTGATTCTTTGTTTGCAATAATTTTGGCCTAGAGACTTCAAATAGTAGCACACATTA AGAACCTGTTACAGCTCATTGTTGAGCTGAATTTTTCCTTTTTGTATTTTCTTAGCAGAGCT CCTGGTGATGTAGAGTATAAAACAGTTGTAACAAGACAGCTTTCTTAGTCATTTTGATCATG AGGGTTAAATATTGTAATATGGATACTTGAAGGACTTTATATAAAAGGATGACTCAAAGGAT TATGGGATAAAAGGCCACAGGAAATAAGACTGCTGAATGTCTGAGAGAACCAGAGTTGTTCT CGTCCAAGGTAGAAAGGTACGAAGATACAATACTGTTATTCATTTATCCTGTACAATCATCT GTGAAGTGGTGGTGAGGTGAGAAGGCGTCCACAAAAGGGGGAGAAAAGGCGACGAATCA GGACACAGTGAACTTGGGAATGAAGAGGTAGCAGGAGGGTGGAGTGTCGGCTGCAAAGGCAG CAGTAGCTGAGCTGCTGCAGGTGCTGATAGCCTTCAGGGGAGGACCTGCCCAGGTATGCCT TCCAGTGATGCCCACCAGAGAATACATTCTCTATTAGTTTTTAAAGAGTTTTTTGTAAAATGA TGTCTATCAAATACCTCTGTAGTAAAATGTGAAAAAGCAAAA

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FIGURE 161

MGFNLTFHLSYKFRLLLLTLCLTVVGWATSNYFVGAIQEIPKAKEFMANFHKTLILGKGKT
LTNEASTKKVELDNCPSVSPYLRGQSKLIFKPDLTLEEVQAENPKVSRGRYRPQECKALQRV
AILVPHRNREKHLMYLLEHLHPFLQRQQLDYGIYVIHQAEGKKFNRAKLLNVGYLEALKEEN
WDCFIFHDVDLVPENDFNLYKCEEHPKHLVVGRNSTGYRLRYSGYFGGVTALSREQFFKVNG
FSNNYWGWGGEDDDLRLRVELQRMKISRPLPEVGKYTMVFHTRDKGNEVNAERMKLLHQVSR
VWRTDGLSSCSYKLVSVEHNPLYINITVDFWFGA

Important features:

Signal peptide:

amino acids 1-27

N-glycosylation sites:

amino acids 4-7, 220-223 and 335-338

Xylose isomerase proteins:

amino acids 191-201

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FIGURE 162

CGTGGGCCGGGGTCGCGCAGCGGGCTGTGGGCGCCCCGGAGGAGCGACCGCCGCAGTTCTC GAGCTCCAGCTGCATTCCCTCCGCGTCCGCCCCACGCTTCTCCCGCTCCGGGCCCCGCAATG CCCGGCAGGGGTGGCCGCAGGCCTGTATGAACTCAATCTCACCACCGATAGCCCTGCCACCA CGGGAGCGGTGGTGACCATCTCGGCCAGCCTGGTGGCCAAGGACAACGGCAGCCTGGCCCTG CCCGCTGACGCCCACCTCTACCGCTTCCACTGGATCCACACCCCGCTGGTGCTTACTGGCAA GATGGAGAAGGGTCTCAGCTCCACCATCCGTGTGGTCGGCCACGTGCCCGGGGAATTCCCGG TCTCTGTCTGGGTCACTGCCGCTGACTGCTGGATGTGCCAGCCTGTGGCCAGGGGCTTTGTG GTCCTCCCATCACAGAGTTCCTCGTGGGGGACCTTGTTGTCACCCAGAACACTTCCCTACC GCAACTTCCTCAAGACCGCCTTGTTTCTCTACAGCTGGGACTTCGGGGACGGGACCCAGATG GTGACTGAAGACTCCGTGGTCTATTATAACTATTCCATCATCGGGACCTTCACCGTGAAGCT CAAAGTGGTGGCGGAGTGGGAAGAGGTGGAGCCGGATGCCACGAGGGCTGTGAAGCAGAAGA CCGGGGACTTCTCCGCCTCGCTGAAGCTGCAGGAAACCCTTCGAGGCATCCAAGTGTTGGGG CCCACCCTAATTCAGACCTTCCAAAAGATGACCGTGACCTTGAACTTCCTGGGGAGCCCTCC TCTGACTGTGTGCTGGCGTCTCAAGCCTGAGTGCCTCCCGCTGGAGGAAGGGGAGTGCCACC CTGTGTCCGTGGCCAGCACAGCGTACAACCTGACCCACACCTTCAGGGACCCTGGGGACTAC TGCTTCAGCATCCGGGCCGAGAATATCATCAGCAAGACACATCAGTACCACAAGATCCAGGT GTGGCCCTCCAGAATCCAGCCGGCTGTCTTTGCTTTCCCATGTGCTACACTTATCACTGTGA TGTTGGCCTTCATCATGTACATGACCCTGCGGAATGCCACTCAGCAAAAGGACATGGTGGAG AACCCGGAGCCACCCTCTGGGGTCAGGTGCTGCTGCCAGATGTGCTGTGGGCCTTTCTTGCT GGAGACTCCATCTGAGTACCTGGAAATTGTTCGTGAGAACCACGGGCTGCTCCCGCCCCTCT ATAAGTCTGTCAAAACTTACACCGTG**TGA**GCACTCCCCCTCCCCACCCCATCTCAGTGTTAA CTGACTGCTGACTTGGAGTTTCCAGCAGGGTGGTGTGCACCACTGACCAGGAGGGGTTCATT TGCGTGGGGCTGTTGGCCTGGATCATCCATCCATCTGTACAGTTCAGCCACTGCCACAAGCC CCTCCCTCTCTGTCACCCCTGACCCCAGCCATTCACCCATCTGTACAGTCCAGCCACTGACA TAAGCCCCACTCGGTTACCACCCCCTTGACCCCCTACCTTTGAAGAGGCTTCGTGCAGGACT TTGATGCTTGGGGTGTTCCGTGTTGACTCCTAGGTGGGCCTGGCCCACTGCCCATTCCT CTCATATTGGCACATCTGCTGTCCATTGGGGGTTCTCAGTTTCCTCCCCCAGACAGCCCTAC CTGTGCCAGAGAGCTAGAAAGAAGGTCATAAAGGGTTAAAAATCCATAACTAAAGGTTGTAC CACACACACAGAAATATAAACACATGCGTCACATGGGCATTTCAGATGATCAGCTCTGTA TCTGGTTAAGTCGGTTGCTGGGATGCACCCTGCACTAGAGCTGAAAGGAAATTTGACCTCCA AGCAGCCCTGACAGGTTCTGGGCCCGGGCCCTCCCTTTGTGCTTTGTCTCTGCAGTTCTTGC GCCCTTTATAAGGCCATCCTAGTCCCTGCTGGCTGGCAGGGCCCTGGATGGGGGGCAGGACT AATACTGAGTGATTGCAGAGTGCTTTATAAATATCACCTTATTTTATCGAAACCCATCTGTG AAACTTTCACTGAGGAAAAGGCCTTGCAGCGGTAGAAGAGGTTGAGTCAAGGCCGGGCGCG TGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGTGGATCACGAGATCAGGA AGCCGGGCGTGGTGGTGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATG GTGCGAACCCGGGAGGCGGAGCTTGCAGTGAGCCCAGATGGCGCCACTGCACTCCAGCCTGA GTGACAGAGCGAGACTCTGTCTCCA

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FIGURE 163

MAQAVWSRLGRILWLACLLPWAPAGVAAGLYELNLTTDSPATTGAVVTISASLVAKDNGSLA
LPADAHLYRFHWIHTPLVLTGKMEKGLSSTIRVVGHVPGEFPVSVWVTAADCWMCQPVARGF
VVLPITEFLVGDLVVTQNTSLPWPSSYLTKTVLKVSFLLHDPSNFLKTALFLYSWDFGDGTQ
MVTEDSVVYYNYSIIGTFTVKLKVVAEWEEVEPDATRAVKQKTGDFSASLKLQETLRGIQVL
GPTLIQTFQKMTVTLNFLGSPPLTVCWRLKPECLPLEEGECHPVSVASTAYNLTHTFRDPGD
YCFSIRAENIISKTHQYHKIQVWPSRIQPAVFAFPCATLITVMLAFIMYMTLRNATQQKDMV
ENPEPPSGVRCCCOMCCGPFLLETPSEYLEIVRENHGLLPPLYKSVKTYTV

Important features of the protein:

Signal peptide:

amino acids 1-24

Transmembrane domain:

amino acids 339-362

N-glycosylation sites.

amino acids 34-37, 58-61, 142-145, 197-200, 300-303 and 364-367

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FIGURE 164

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FIGURE 165

MALSSQIWAACLLLLLLASLTSGSVFPQQTGQLAELQPQDRAGARASWMPMFQRRRRRDTH FPICIFCCGCCHRSKCGMCCKT

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FIGURE 166

-CTGTCAGGAAGGACCATCTGAAGGCTGCAATTTGTTCTTAGGGAGGCAGGTGCTGGCCTGGC CTGGATCTTCCACCATGTTCCTGTTGCTGCCTTTTGATAGCCTGATTGTCAACCTTCTGGGC AGTCTCCTTTGGTATCCGCAAACTCTACATGAAAAGTCTGTTAAAAATCTTTGCGTGGGCTA CCTTGAGAATGGAGCGAGGAGCCAAGGAGAAGAACCACCAGCTTTACAAGCCCTACACCAAC GGAATCATTGCAAAGGATCCCACTTCACTAGAAGAGATCAAAGAGATTCGTCGAAGTGG TAGTAGTAAGGCTCTGGACAACACTCCAGAGTTCGAGCTCTCTGACATTTTCTACTTTTGCC GGAAAGGAATGGAGACCATTATGGATGATGAGGTGACAAAGAGATTCTCAGCAGAAGAACTG GAGTCCTGGAACCTGCTGAGCAGAACCAATTATAACTTCCAGTACATCAGCCTTCGGCTCAC GGTCCTGTGGGGGTTAGGAGTGCTGATTCGGTACTGCTTTCTGCTGCCGCTCAGGATAGCAC TGGCTTTCACAGGGATTAGCCTTCTGGTGGTGGGCACAACTGTGGTGGGATACTTGCCAAAT AGCGCTGACAGCCATCATCACCTACCATGACAGGGAAAACAGACCAAGAAATGGTGGCATCT GTGTGGCCAATCATACCTCACCGATCGATGTGATCATCTTGGCCAGCGATGGCTATTATGCC ATGGTGGGTCAAGTGCACGGGGGACTCATGGGTGTGATTCAGAGAGCCATGGTGAAGGCCTG CCCACACGTCTGGTTTGAGCGCTCGGAAGTGAAGGATCGCCACCTGGTGGCTAAGAGACTGA CTGAACATGTGCAAGATAAAAGCAAGCTGCCTATCCTCATCTTCCCAGAAGGAACCTGCATC AATAATACATCGGTGATGATGTTCAAAAAGGGAAGTTTTGAAATTGGAGCCACAGTTTACCC TGTTGCTATCAAGTATGACCCTCAATTTGGCGATGCCTTCTGGAACAGCAGCAAATACGGGA TGGTGACGTACCTGCGAATGATGACCAGCTGGGCCATTGTCTGCAGCGTGTGGTACCTG CCTCCCATGACTAGAGAGGCAGATGAAGATGCTGTCCAGTTTGCGAATAGGGTGAAATCTGC CATTGCCAGGCAGGAGGACTTGTGGACCTGCTGTGGGATGGGGGCCTGAAGAGGGAGAAGG TGAAGGACACGTTCAAGGAGGAGCAGCAGAAGCTGTACAGCAAGATGATCGTGGGGAACCAC AAGGACAGGAGCCGCTCC<u>TGA</u>GCCTGCCTCCAGCTGGCGGGCCCACCGTGCGGGGTGCCAA CGGGCTCAGAGCTGGAGTTGCCGCCGCCGCCCCCCTGCTGTCCTTTCCAGACTCCAGGG CTCCCGGGCTGCTCTGGATCCCAGGACTCCGGCTTTCGCCGAGCCGCAGCGGGATCCCTGT GCACCCGGCGCAGCCTACCCTTGGTGGTCTAAACGGATGCTGCTGGGTGTTGCGACCCAGGA CGAGATGCCTTGTTTCTTTTACAATAAGTCGTTGGAGGAATGCCATTAAAGTGAACTCCCCA CCTTTGCACGCTGTGCGGGCTGAGTGGTTGGGGAGATGTGGCCATGGTCTTGTGCTAGAGAT GGCGGTACAAGAGTCTGTTATGCAAGCCCGTGTGCCAGGGATGTGCTGGGGGGCGGCCACCCG CTCTCCAGGAAAGGCACAGCTGAGGCACTGTGGCTGGCTTCGGCCTCAACATCGCCCCCAGC CTTGGAGCTCTGCAGACATGATAGGAAGGAAACTGTCATCTGCAGGGGCTTTCAGCAAAATG GGCCGCTGACTGGGCCATGGGGAACGTGTGTTCGTACTCCAGGCTAACCCTGAACTCCCC ATGTGATGCGCGCTTTGTTGAATGTGTCTCGGTTTCCCCATCTGTAATATGAGTCGGGGG AGGACACATCACGTTCAGTGTTTCAAGTACAGGCCCACAAAACGGGGCACGGCAGGCCTGAG TGA

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FIGURE 167

MFLLLPFDSLIVNLLGISLTVLFTLLLVFIIVPAIFGVSFGIRKLYMKSLLKIFAWATLRME
RGAKEKNHQLYKPYTNGIIAKDPTSLEEEIKEIRRSGSSKALDNTPEFELSDIFYFCRKGME
TIMDDEVTKRFSAEELESWNLLSRTNYNFQYISLRLTVLWGLGVLIRYCFLLPLRIALAFTG
ISLLVVGTTVVGYLPNGRFKEFMSKHVHLMCYRICVRALTAIITYHDRENRPRNGGICVANH
TSPIDVIILASDGYYAMVGQVHGGLMGVIQRAMVKACPHVWFERSEVKDRHLVAKRLTEHVQ
DKSKLPILIFPEGTCINNTSVMMFKKGSFEIGATVYPVAIKYDPQFGDAFWNSSKYGMVTYL
LRMMTSWAIVCSVWYLPPMTREADEDAVQFANRVKSAIARQGGLVDLLWDGGLKREKVKDTF
KEEOOKLYSKMIVGNHKDRSRS

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FIGURE 168

GCCCTCGAAACCAGGACTCCAGCACCTCTGGTCCCGCCCTCACCCGGACCCCTGGCCCTCA CGTCTCCTCCAGGGATGCCGCTGGCGGCTTTGATGATCGCCCTCGGCAGCCTCGGCCTCCAC ACCTGGCAGGCCCAGGCTGTTCCCACCATCCTGCCCCTGGGCCTGGCTCCAGACACCTTTGA CGATACCTATGTGGGTTGTGCAGAGGAGATGGAGGAGAAGGCAGCCCCCTGCTAAAGGAGG AAATGGCCCACCATGCCCTGCTGCGGGAATCCTGGGAGGCCCAGGAGACCTGGGAGGAC AAGCGTCGAGGGCTTACCTTGCCCCCTGGCTTCAAAGCCCAGAATGGAATAGCCATTATGGT CTACACCAACTCATCGAACACCTTGTACTGGGAGTTGAATCAGGCCGTGCGGACGGGCGGAG GCTCCCGGGAGCTCTACATGAGGCACTTTCCCTTCAAGGCCCTGCATTTCTACCTGATCCGG GCCCTGCAGCTGCGAGGCAGTGGGGGGCTGCAGCAGGGGACCTGGGGAGGTGGTGTTCCG AGGTGTGGGCAGCCTTCGCTTTGAACCCAAGAGGCTGGGGGACTCTGTCCGCTTGGGCCAGT TTGCCTCCAGCTCCCTGGATAAGGCAGTGGCCCACAGATTTGGGGAGAAGAGGCGGGGCTGT GTGTCTGCGCCAGGGGTGCAGCTAGGGTCACAATCTGAGGGGGCCTCCTCTCTGCCCCCCTG GAAGACTCTGCTCTTGGCCCCTGGAGAGTTCCAGCTCTCAGGGGTTGGGCCC**TGA**AAGTCCA ACATCTGCCACTTAGGAGCCCTGGGAACGGGTGACCTTCATATGACGAAGAGGCACCTCCAG CAGCCTTGAGAAGCAAGAACATGGTTCCGGACCCAGCCCTAGCAGCCTTCTCCCCAACCAGG ATGTTGGCCTGGGGAGGCCACAGCAGGGCTGAGGGAACTCTGCTATGTGATGGGGACTTCCT TGGAGTTTTATTGAGGTAGCTACGTGATTAAATGGTATTGCAGTGTGGA

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FIGURE 169

MALAALMIALGSLGLHTWQAQAVPTILPLGLAPDTFDDTYVGCAEEMEEKAAPLLKEEMAHH ALLRESWEAAQETWEDKRRGLTLPPGFKAQNGIAIMVYTNSSNTLYWELNQAVRTGGGSREL YMRHFPFKALHFYLIRALQLLRGSGGCSRGPGEVVFRGVGSLRFEPKRLGDSVRLGQFASSS LDKAVAHRFGEKRRGCVSAPGVQLGSQSEGASSLPPWKTLLLAPGEFQLSGVGP

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FIGURE 170

GTGGCTTCATTTCAGTGGCTGACTTCCAGAGAGCAAT<u>ATG</u>GCTGGTTCCCCAACATGCCTCA CCCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGCTG GTCGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTCCAAAGTAAAGCAAGTTGACTC TATTGTCTGGACCTTCAACACCCCTCTTGTCACCATACAGCCAGAAGGGGGCACTATCA TAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCCTGAAG CTCAGCAAACTGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTCATCACT CCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAGCCTAAAG TCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACATGCTGCATG GAACATGGGGAAGAGGTGTGATTTATACCTGGAAGGCCCTGGGGCAAGCAGCCAATGAGTC CCATAATGGGTCCATCCCCCATCTCCTGGAGATGGGGAGAAAGTGATATGACCTTCATCT GCGTTGCCAGGAACCCTGTCAGCAGAAACTTCTCAAGCCCCATCCTTGCCAGGAAGCTCTGT GAAGGTGCTGCTGATGACCCAGATTCCTCCATGGTCCTCCTGTGTCTCCTGTTGGTGCCCCT AGTACATTGAAGAGAGAGAGAGTGGACATTTGTCGGGAAACTCCTAACATATGCCCCCAT TCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAATAGAACAATCCTAAAGGAAGA TCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAAAGATGGAAAATCCCCACTCAC TGCTCACGATGCCAGACACACGAGGCTATTTGCCTATGAGAATGTTATCTAGACAGCAGTG CACTCCCCTAAGTCTCTGCTCA

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FIGURE 171

MAGSPTCLTLIYILWQLTGSAASGPVKELVGSVGGAVTFPLKSKVKQVDSIVWTFNTTPLVT
IQPEGGTIIVTQNRNRERVDFPDGGYSLKLSKLKKNDSGIYYVGIYSSSLQQPSTQEYVLHV
YEHLSKPKVTMGLQSNKNGTCVTNLTCCMEHGEEDVIYTWKALGQAANESHNGSILPISWRW
GESDMTFICVARNPVSRNFSSPILARKLCEGAADDPDSSMVLLCLLLVPLLLSLFVLGLFLW
FLKRERQEEYIEEKKRVDICRETPNICPHSGENTEYDTIPHTNRTILKEDPANTVYSTVEIP
KKMENPHSLLTMPDTPRLFAYENVI

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FIGURE 172

CTGGTTCCCCAACATGCCTCACCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCC TCTGGACCCGTGAAAGAGCTGGTCGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTC CAAAGTAAAGCAAGTTGACTCTATTGTCTGGACCTTCAACACAACCCCTCTTGTCACCATAC AGCCAGAAGGGGGCACTATCATAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCA GATGGAGGCTACTCCCTGAAGCTCAGCAAACTGAAGAAGAATGACTCAGGGATCTACTATGT GGGGATATACAGCTCATCACTCCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACG AGCACCTGTCAAAGCCTAAAGTCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTG ACCAATCTGACATGCTGCATGGAACATGGGGAAGAGGATGTGATTTATACCTGGAAGGCCCT GGGGCAAGCAGCCAATGAGTCCCATAATGGGTCCATCCTCCCCATCTCCTGGAGATGGGGAG AAAGTGATATGACCTTCATCTGCGTTGCCAGGAACCCTGTCAGCAGAAACTTCTCAAGCCCC ATCCTTGCCAGGAAGCTCTGTGAAGGTGCTGCTGATGACCCAGATTCCTCCATGGTCCTCCT GTGTCTCCTGTTGGTGCCCCTCCTGCTCAGTCTCTTTGTACTGGGGCTATTTCTTTGGTTTC ACTCCTAACATATGCCCCCATTCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAA TAGAACAATCCTAAAGGAAGATCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAA AGATGGAAAATCCCCACTCACTGCTCACGATGCCAGACACACCAAGGCTATTTGCCTATGAG

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FIGURE 173

GAAAGACGTGGTCCTGACAGACAGACAATCCTATTCCCTACCAAAATGAAGATGCTGCTGCT
GCTGTGTTTGGGACTGACCCTAGTCTGTGTCCATGCAGAAGAAGCTAGTTCTACGGGAAGGA
ACTTTAATGTAGAAAAGATTAATGGGGAATGGCATACTATTATCCTGGCCTCTGACAAAAGA
GAAAAGATAGAAGAACATGGCAACTTTAGACTTTTTCTGGAGCAAATCCATGTCTTGGAGAA
TTCCTTAGTTCTTAAAGTCCATACTGTAAGAGATGAAGAGTGCTCCGAATTATCTATGGTTG
CTGACAAAACAGAAAAGGCTGGTGAATATTCTGTGACGTATGATGGATTCAATACATTTACT
ATACCTAAGACAGACTATGATAACTTTCTTTATGGCTCACCTCATTAACGAAAAGGATGGGGA
AACCTTCCAGCTGATGGGGCCTCTATGGCCGAGAACCAGATTTGAGTTCAGACATCAAGGAAA
GGTTTGCACAACTATGTGAGGAGCATGGAATCCTTAGAGAAAATATCATTGACCTATCCAAT
GCCAATCGCTGCCTCCAGGCCCGAGAATGAAGAATGGCCTGAGCCTCCAGTGTTGAGTGGAC
ACTTCTCACCAGGACTCCACCATCATCCCTTCCTATCCATACAGCATCCCCAGTATAAATTC
TGTGATCTGCATTCCATCCTGTCTCACTGAGAAGTCCAATTCCAGTCTATCAACATGTTACC
TAGGATACCTCATCAAGAATCAAAGACTTCTTTAAATTTCTCTTTGATACACCCTTGACAAT
TTTTCATGAAATTATTCCTCTTTCCTGTTCAATAAATGATTACCCTTGCACTTAA

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FIGURE 174

MKMLLLCLGLTLVCVHAEEASSTGRNFNVEKINGEWHTIILASDKREKIEEHGNFRLFLEQ IHVLENSLVLKVHTVRDEECSELSMVADKTEKAGEYSVTYDGFNTFTIPKTDYDNFLMAHLI NEKDGETFQLMGLYGREPDLSSDIKERFAQLCEEHGILRENIIDLSNANRCLQARE

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FIGURE 175

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FIGURE 176

MTCCEGWTSCNGFSLLVLLLLGVVLNAIPLIVSLVEEDQFSQNPISCFEWWFPGIIGAGLMA IPATTMSLTARKRACCNNRTGMFLSSFFSVITVIGALYCMLISIQALLKGPLMCNSPSNSNA NCEFSLKNISDIHPESFNLQWFFNDSCAPPTGFNKPTSNDTMASGWRASSFHFDSEENKHRL IHFSVFLGLLLVGILEVLFGLSQIVIGFLGCLCGVSKRRSQIV

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FIGURE 177

GTCGAATCCAAATCACTCATTGTGAAAGCTGAGCTCACAGCCGAATAAGCCACCATGATGAGGCT
GTCAGTGTGTCTCCTGATGGTCTCGCTGGCCCTTTGCTGCTACCAGGCCCATGCTCTTGTCT
GCCCAGCTGTTGCTTCTGAGATCACAGTCTTCTTATTCTTAAGTGACGCTGCGGTAAACCTC
CAAGTTGCCAAACTTAATCCACCTCCAGAAGCTCTTGCAGCCAAGTTGGAAGTGAAGCACTG
CACCGATCAGATATCTTTTAAGAAACGACTCTCATTGAAAAAAGTCCTGGTGGAAATAGTGAA
AAAATGTGGTGTGACATGTAAAAATGCTCAACCTGGTTTCCAAAGTCTTTCAACGACACC
CTGATCTTCACTAAAAATTGTAAAGGTTTCAACACGTTGCTTTAATAAATCACTTGCCCTGC

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FIGURE 178

MRLSVCLLMVSLALCCYQAHALVCPAVASEITVFLFLSDAAVNLQVAKLNPPPEALAAKLEV KHCTDQISFKKRLSLKKSWWK

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FIGURE 179

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FIGURE 180

MERVTLALLLLAGLTALEANDPFANKDDPFYYDWKNLQLSGLICGGLLAIAGIAAVLSGKCK YKSSQKQHSPVPEKAIPLITPGSATTC

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FIGURE 181

GGAGAAGAGGTTGTGTGGGACAAGCTGCTCCCGACAGAAGGATGTCGCTGCTGAGCCTGCCC TGGCTGGGCCTCAGACCGGTGGCAATGTCCCCATGGCTACTCCTGCTGCTGGTTGTGGGCTC CTGGCTACTCGCCCGCATCCTGGCTTGGACCTATGCCTTCTATAACAACTGCCGCCGGCTCC AGTGTTTCCCACAGCCCCCAAAACGGAACTGGTTTTGGGGTCACCTGGGCCTGATCACTCCT ACAGAGGAGGGCTTGAAGGACTCGACCCAGATGTCGGCCACCTATTCCCAGGGCTTTACGGT ATGGCTGGGTCCCATCATCCCTTCATCGTTTTATGCCACCCTGACACCATCCGGTCTATCA CCAATGCCTCAGCTGCCATTGCACCCAAGGATAATCTCTTCATCAGGTTCCTGAAGCCCTGG CTGGGAGAAGGGATACTGCTGAGTGGCGGTGACAAGTGGAGCCGCCACCGTCGGATGCTGAC GCCCGCCTTCCATTTCAACATCCTGAAGTCCTATATAACGATCTTCAACAAGAGTGCAAACA TCATGCTTGACAAGTGGCAGCACCTGGCCTCAGAGGGCAGCAGTCGTCTGGACATGTTTGAG CACATCAGCCTCATGACCTTGGACAGTCTACAGAAATGCATCTTCAGCTTTGACAGCCATTG TCAGGAGAGGCCCAGTGAATATATTGCCACCATCTTGGAGCTCAGTGCCCTTGTAGAGAAAA GAAGCCAGCATATCCTCCAGCACATGGACTTTCTGTATTACCTCTCCCATGACGGCGGCGC TTCCACAGGGCCTGCCGCCTGGTGCATGACTTCACAGACGCTGTCATCCGGGAGCGGCGTCG CACCCTCCCCACTCAGGGTATTGATGATTTTTTCAAAGACAAAGCCAAGTCCAAGACTTTGG ATTTCATTGATGTGCTTCTGCTGAGCAAGGATGAAGATGGGAAGGCATTGTCAGATGAGGAT ATAAGAGCAGAGGCTGACACCTTCATGTTTGGAGGCCATGACACCACGGCCAGTGGCCTCTC CTGGGTCCTGTACAACCTTGCGAGGCACCCAGAATACCAGGAGCGCTGCCGACAGGAGGTGC AAGAGCTTCTGAAGGACCGCGATCCTAAAGAGATTGAATGGGACGACCTGGCCCAGCTGCCC TTCCTGACCATGTGCGTGAAGGAGACCTGAGGTTACATCCCCCAGCTCCCTTCATCTCCCG ATGCTGCACCCAGGACATTGTTCTCCCAGATGGCCGAGTCATCCCCAAAGGCATTACCTGCC TCATCGATATTATAGGGGTCCATCACAACCCAACTGTGTGGCCGGATCCTGAGGTCTACGAC CCCTTCCGCTTTGACCCAGAGAACAGCAAGGGGAGGTCACCTCTGGCTTTTATTCCTTTCTC CGCAGGGCCCAGGAACTGCATCGGGCAGGCGTTCGCCATGGCGGAGATGAAAGTGGTCCTGG CGTTGATGCTGCACTTCCGGTTCCTGCCAGACCACACTGAGCCCCGCAGGAAGCTGGAA TTGATCATGCGCCCGAGGGCGGGCTTTGGCTGCGGGTGGAGCCCCTGAATGTAGGCTTGCA **GTGA**CTTTCTGACCCATCCACCTGTTTTTTTGCAGATTGTCATGAATAAAACGGTGCTGTCAAA

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FIGURE 182

MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLARILAWTYAFYNNCRRLQCFPQPPKRNWFWG
HLGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIPFIVLCHPDTIRSITNASAAIAPKDNLF
IRFLKPWLGEGILLSGGDKWSRHRRMLTPAFHFNILKSYITIFNKSANIMLDKWQHLASEGS
SRLDMFEHISLMTLDSLQKCIFSFDSHCQERPSEYIATILELSALVEKRSQHILQHMDFLYY
LSHDGRRFHRACRLVHDFTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFIDVLLLSKDEDG
KALSDEDIRAEADTFMFGGHDTTASGLSWVLYNLARHPEYQERCRQEVQELLKDRDPKEIEW
DDLAQLPFLTMCVKESLRLHPPAPFISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNPTVW
PDPEVYDPFRFDPENSKGRSPLAFIPFSAGPRNCIGQAFAMAEMKVVLALMLLHFRFLPDHT
EPRRKLELIMRAEGGLWLRVEPLNVGLQ

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FIGURE 183

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FIGURE 184

MYKLASCCLLFTGFLNPLLSLPLLDSREISFQLSAPHEDARLTPEELERASLLQILPEMLGA ERGDILRKADSSTNIFNPRGNLRKFQDFSGQDPNILLSHLLARIWKPYKKRETPDCFWKYCV

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FIGURE 185

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FIGURE 186

MPSPGTVCSLLLLGMLWLDLAMAGSSFLSPEHQRVQQRKESKKPPAKLQPRALAGWLRPEDG GQAEGAEDELEVRFNAPFDVGIKLSGVQYQQHSQALGKFLQDILWEEAKEAPADKO

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FIGURE 187

CGGCCACAGCTGGCATGCTCTGCCTGATCGCCATCCTGCTGTATGTCCTCGTCCAGTACCTC GTGAACCCCGGGGTGCTCCGCACGGACCCCAGATGTCAAGAATATGAACACGTGGCTGCTGT TCCTCCCCTGTTCCCGGTGCAGGTGCAGACCCTGATAGTCGTGATCATCGGGATGCTCGTG CTCCTGCTGGACTTCTTGGCTTGGTGCACCTGGGCCAGCTGCTCATCTTCCACATCTACCT TTACACCTCTACTTGAGTATGTCCCTAACCCTGAGCCCCCACGCCTGGGGCCAGAGTCTTT GTCCCCGTGTGCGCATGTGTTCAGGGTCAGCCTCTCCCAGAAGTGAGATCATGGACAAAAA GGGCAAATCACAGGAAGAAATTAAATCCATGAGGACCCAGCAGGCCCAGCAAGAAGCTGAAC TCACGCCGAGACCTGCAGGAGTGGTGCCAGGTGCTTGAAGTAACAAGTTTAAAATGTTCAGA GACAATGGAATGGAATCTATTAGGCAAGAACAGGACATTATGAAATAAGGACAGGTGGACTT AACAACTGAAGCGAGAGCTGTGGTCTTGCTTGGTCTCACAGTGGGCACAGCGGTAGGCGGTC AGTCATGTTGCTGAACGACGGAGGGTAAACTCCCCAGCCCCAAGAAAACCTGTGTTGGAAGT AACAACAACCTCCCTGCTCCTGGCACCAGCCGTTTTGGTCATGGTGGGCCAGCTGCAAAGCG TCTTCCATTCTCTGGGCAGTGGTGGCCCCGAGGCTGTGGCCTCTCAGGGGGTTTCTGTGGAC ACGGCCAGCAGAGTGTGTCCAGGCCAGCCCCCAAGAATGCCCTGCTCCTGACAGCTTGGCCA ACCCTGGTCAGGGCAGAGGGAGTTGGGTGGGTCAGGCTCTGGGCTCACCTCCATCTCCAGA GCATCCCCTGCCTGCAGTTGTGGCAAGAACGCCCAGCTCAGAATGAACACACCCCACCAAGA GCCTCCTTGTTCATAACCACAGGTTACCCTACAAACCACTGTCCCCACACAACCCTGGGGAT GTTTTAAAACACACCTCTAACGCATATCTTACAGTCACTGTTGTCTTGCCTGAGGGTTGA ATTTTTTTAATGAAAGTGCAATGAAAATCACTGGATTAAATCCTACGGACACAGAGCTGAA ΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑ

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FIGURE 188

MNTWLLFLPLFPVQVQTLIVVIIGMLVLLLDFLGLVHLGQLLIFHIYLSMSPTLSPRSPQGW VVRAAHLTPLLEYVPNPEPPTPGARVFVPRVRMCSGSASPRSEIMDKKGKSQEEIKSMRTQQ AQQEAELTPRPAGVVPGA

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FIGURE 189

GGAGTGCAGATGGCATCCTTCGGTTCTTCCAGACAAGCTGCAAGACGCTGACCATGGCCAAG ATGGAGCTCTCGAAGGCCTTCTCTGGCCAGCGGACACTCCTATCTGCCATCCTCAGCATGCT ATCACTCAGCTTCTCCACAACATCCCTGCTCAGCAACTACTGGTTTGTGGGCACACAGAAGG TGCCCAAGCCCTGTGCGAGAAAGGTCTGGCAGCCAAGTGCTTTGACATGCCAGTGTCCCTG GATGGAGATACCAACACATCCACCCAGGAGGTGGTACAATACAACTGGGAGACTGGGGATGA CCGGTTCTCCTTCCGGAGCTTCCGGAGTGGCATGTGGCTATCCTGTGAGGAAACTGTGGAAG GGACTACTGGAATTTGCCACGTTGCAAGGCCCATGTCACCCCACTCTCCGATTTGGAGGGAA GCGGTTGATGGAGAAGGCTTCCCTCCCCTCCCTTGGGGGCTTTGTGGCAAAAATCCTA TGGTTATCCCTGGGAACGCAGATCACCTACATCGGACTTCAATTCATCAGCTTCCTCCTGCT ACTAACAGACTTGCTACTCACTGGGAACCCTGCCTGTGGGCTCAAACTGAGCGCCTTTGCTG CTGTTTCCTCTGTCAGGTCTCCTGGGGATGGTGGCCCACATGATGTATTCACAAGTC TTCCAAGCGACTGTCAACTTGGGTCCAGAAGACTGGAGACCACATGTTTGGAATTATGGCTG GGCCTTCTACATGGCCTGGCTCTCCTTCACCTGCTGCATGGCGTCGGCTGTCACCACCTTCA ACACGTACACCAGGATGGTGCTGGAGTTCAAGTGCAAGCA**TAG**TAAGAGCTTCAAGGAAAAC CCGAACTGCCTACCACATCACCATCAGTGTTTCCCTCGGCGGCTGTCAAGTGCAGCCCCCAC CGTGGGTCCTTTGACCACCACCACTATCATAATCAGCCCATCCACTCTGTCTCTGAGG AAAGAAGCAGTTAGGTCATCTGTAGAGGAAGAGCAGTGTTAGGAGTTAAGCGGGTTTGGGGA GTAGGCTTGAGCCCTACCTTACACGTCTGCTGATTATCAACATGTGCTTAAGCCAACATCCG TCTCTTGAGCATGGTTTTTAGAGGCTACGAATAAGGCTATGAATAAGGGTTATCTTTAAGTC CTAAGGGATTCCTGGGTGCCACTGCTCTTTTCCTCTACAGCTCCATCTTGTTTCACCCAC CCCACATCTCACACATCCAGAATTCCCTTCTTTACTGATAGTTTCTGTGCCAGGTTCTGGGC TAAACCATGGAGATAAAAAGAAGAGTAAAATACACTTCCCGACCTTAAGGATCTGAAA

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FIGURE 190

MAKMELSKAFSGQRTLLSAILSMLSLSFSTTSLLSNYWFVGTQKVPKPLCEKGLAAKCFDMP VSLDGDTNTSTQEVVQYNWETGDDRFSFRSFRSGMWLSCEETVEEPGERCRSFIELTPPAKR GEKGLLEFATLQGPCHPTLRFGGKRLMEKASLPSPPLGLCGKNPMVIPGNADHLHRTSIHQL PPATNRLATHWEPCLWAQTERLCCCFLCPVRSPGDGGPHDVFTSLPSDCQLGSRRLETTCLE LWLGLLHGLALLHLLHGVGCHHLQHVHQDGAGVQVQA

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FIGURE 191

AACTGGAAGGAAAGAAAGATCAGCTTTGGCCCAG<u>ATG</u>TGGTTACCCCTTGGTCTCCTG TCTTTATGTCTTTCTCCTCTTCCTATTCTGTCATCTCCCTCACTTAAGTCTCAGGCCTGTCA GCAGCTCCTGTGGACATTGCCATCCCCTCTGGTAGCCTTCAGAGCAAACAGGACAACCTATG TTATGGATGTTTCCACCAACCAGGGTAGTGGCATGGAGCACCGTAACCATCTGTGCTTCTGT GATCTCTATGACAGAGCCACTTCTCCACCTCTGAAATGTTCCCTGCTCTGAAATCTGGCATG GTCTGTTCTCTTATTGTCAACCTCAGCACAACAGGCTGGCGCCAATGGCATTACAGAGAAAG CAATCTGTGTGGCTAGTGGGCAGATTACCATGCAAGCCCCAGGAGAAATGGAGGAGCTTTGT AGCCACCTCCCTGTCAGCCAGTATTAACATGTCCCCTTCCCCCTGCCCCGCCGTAGATTCAG GACATTCGCCCCTGTGTGCCACCAAACCAGGACTTTCCCCTTGGCTTGGCATCCCTGGCTCT CTCCTGGTACCCAGCAAGACGTCTGTTCCAGGGCAGTGTAGCATCTTTCAAGCTCCGTTACT ATGGCGATGGCCATGATGTTACAATCCCACTTGCCTGAATAATCAAGTGGGAAGGGAAGCA GAGGGAAATGGGGCCATGTGAATGCAGCTGCTCTGTTCTCCCTACCCTGAGGAAAAACCAAA TGTTGAAGGGCACAAGAAATGTAGCTGGAGAAGATTGATGAAAGTGCAGGTGTAAGGAA ATAGAACAGTCTGCTGGGAGTCAGACCTGGAATTCTGATTCCAAACTCTTTATTACTTTGGG AAGTCACTCAGCCTCCCCGTAGCCATCTCCAGGGTGACGGAACCCAGTGTATTACCTGCTGG AACCAAGGAAACTAACAATGTAGGTTACTAGTGAATACCCCAATGGTTTCTCCAATTATGCC CATGCCACCAAAACAATAAAACAAAATTCTCTAACACTGAAA

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FIGURE 192

MWLPLGLLSLCLSPLPILSSPSLKSQACQQLLWTLPSPLVAFRANRTTYVMDVSTNQGSGME HRNHLCFCDLYDRATSPPLKCSLL

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FIGURE 193

CCGCCATGGCAGCATCAAAGCTTTGATTAGTTTGTCCTTTGGAGGAGCAATCGGACTGATGTTTTTGATGCTT GGATGTGCCCTTCCAATATACAACAAATACTGGCCCCTCTTTGTTCTATTTTTTTACATCCTTTCACCTATTCC ATACTGCATAGCAAGAAGATTAGTGGATGATACAGATGCTATGAGTAACGCTTGTAAGGAACTTGCCATCTTTC TTACAACGGCCATTGTCGTGTCAGCTTTTGGACTCCCTATTGTATTTGCCAGAGCACATCTGATTGAGTGGGGA GCTTGTGCACTTGTTCTCACAGGAAACACAGTCATCTTTGCAACTATACTAGGCTTTTTCTTGGTCTTTGGAAG CAATGACGACTTCAGCTGGCAGCAGTGG<u>TGA</u>AAAGAAATTACTGAACTATTGTCAAATGGACTTCCTGTCATTT GTTGGCCATTCACGCACACAGGAGATGGGCAGTTAATGCTGAATGGTATAGCAAGCCTCTTGGGGGTATTTTA GGTGCTCCCTTCTCACTTTTATTGTAAGCATACTATTTTCACAGAGACTTGCTGAAGGATTAAAAGGATTTTCT CTTTTGGAAAAGCTTGACTGATTTCACACTTATCTATAGTATGCTTTTTTGTGGTGTCCTGCTGAATTTAAATAT TTATGTGTTTTTCCTGTTAGGTTGATTTTTTTTGGAATCAATATGCAATGTTAAACACTTTTTTAATGTAATCA TTTGCATTGGTTAGGAATTCAGAATTCCGCCGGCTCTATTACTGGTCAAGTACATCTTTTCTCTTAAAATTATT CAGACATACAGACGGTTGGCATACGTTATAGACTGTATACTCAGTGCAAATATAGCTGCATTTATACCTCAGAG GGGCCAAGTGTTAATGCCCATGCCCTCCGTTAAGGGTTGTTGGTTTTACTGGTAGACAGATGTTTTGTGGATTG AAAATTATTTTATGGAATTGCTACAGAGGAGTGCTTTTCTTCTCAATTGTTAGAAGAATTTATGTTAAACTTTA GGGAAGAAATGACATTGAAATTCCAGTTTTTGAATCCTGTTTCTATTTATAAGTGAAATTTGTGATCTCCTATC AACCTTTCATGTTTTACCCTGTTAAAATGGACATACATGGAACCACTACTGATGAGGGACAGTTGTATGTTTGC CAGAGTGCCCCCTCCCCTGCAAGGCCTTGCCATGATTAACAAGTAACTTGTTAGTCTTACAGATAATTCATGCA TTAACAGTTTAAGATTTAGACCATGGTAATAGTAGTTCTTATTCTCTAAGGTTATATCATATGTAATTTAAAAG TATTTTTAAGACAAGTTTCCTGTATACCTCTGAACTGTTTTGATTTTGAGTTCATCATGATAGATCTGCTGTTT CCTTATAAAAGGCATTTGTTGTGTGAGTTAATGCAAAGTAGCCAAGTCCAGCTATATAGCAGCTTCAGAAACAT ACCTGACCAAAAAATTCCCAGTAACCAGGCATGATCAATTTATAGTGGTCGTTTACATCTAATAATTATCAGGA TTTATGAAGTTTATTTCTCAAGAAAATGGGAATAAATTTGGGATTTGTTCAGCTTTTTTACTAAAGATGCCTAA AGCCACAGGTTTTATTGCCTAACTTAAGCCATGACTTTTAGATATGAGATGACGGGAAGCAGGACGAAATATCG GCGTGTGGCTGGAGCCTTCCCACTGGAGGCTGAAAGTGGCTTGTGGTATTATAATGTTCAGATTTCAAGAGGAA GGTGCAGGTACACATGAGTTAGAGAGCTGGTGAGACAGTTGGGAACTCTTTGTGCTTGTGATCTACTGGACTTT TTTTTTGCAGGAAGTGCATTCTCTGGTCCTTCCCTATTTTCTGTTCTGGATGTCAGTGCAGTGCACTGCTACTG TTTTATCCACTTGGCCACAGACTTTTTCTAACAGCTGCGTATTATTTCTATATACTAATTGCATTGGCAGCATT GTGTCTTTGACCTTGTATACTAGCTTGACATAGTGCTGTCTCTGATTTCTAGGCTAGTTACTTGAGATATGAAT AGATTTTAAATATCTATTTTAAAAAAAAAA

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FIGURE 194

MAGIKALISLSFGGAIGLMFLMLGCALPIYNKYWPLFVLFFYILSPIPYCIARRLVDDTDAM SNACKELAIFLTTGIVVSAFGLPIVFARAHLIEWGACALVLTGNTVIFATILGFFLVFGSND DFSWQQW

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FIGURE 195

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FIGURE 196

MDFLLLGLCLYWLLRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEAPH
NLSGLLGLSLRYNSLSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTLSSNQ
ITQLPNTTFRPMPNLRSVDLSYNKLQALAPDLFHGLRKLTTLHMRANAIQFVPVRIFQDCRS
LKFLDIGYNQLKSLARNSFAGLFKLTELHLEHNDLVKVNFAHFPRLISLHSLCLRRNKVAIV
VSSLDWVWNLEKMDLSGNEIEYMEPHVFETVPHLQSLQLDSNRLTYIEPRILNSWKSLTSIT
LAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDAVYAFHLCEDGAEPTSG
HLLSAVTNRSDLGPPASSATTLADGGEGQHDGTFEPATVALPGGEHAENAVQIHKVVTGTMA
LIFSFLIVVLVLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQMAAMSAQEYYVDYKPNH
IEGALVIINEYGSCTCHQQPARECEV

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FIGURE 197

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FIGURE 198

MGVLGRVLLWLQLCALTQAVSKLWVPNTDFDVAANWSQNRTPCAGGAVEFPADKMVSVLVQE GHAVSDMLLPLDGELVLASGAGFGVSDVGSHLDCGAGEPAVFRDSDRFSWHDPHLWRSGDEA PGLFFVDAERVPCRHDDVFFPPSASFRVGLGPGASPVRVRSISALGRTFTRDEDLAVFLASR AGRLRFHGPGALSVGPEDCADPSGCVCGNAEAQPWICAALLQP

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FIGURE 199

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FIGURE 200

MGPVKQLKRMFEPTRLIATIMVLLCFALTLCSAFWWHNKGLALIFCILQSLALTWYSLSFIP FARDAVKKCFAVCLA

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FIGURE 201

CCGAGGGAGTCTCCTCCAGACCCTCCCTCCCGTTGCTCCAAACTAATACGGACTGAACGGATCGCTGCGAGGGT AACCACCTTTCTCTCCAACTAGACCAGCAAAAGGTTCTACTAGTTTCTTTTGATGGATTCCGTTGGGATTACT TATATAAAGTTCCAACGCCCCATTTTCATTATATTATGAAATATGGTGTTCACGTGAAGCAAGTTACTAATGTT TTTATTACAAAAACCTACCCTAACCATTATACTTTGGTAACTGGCCTCTTTGCAGAGAATCATGGGATTGTTGC **AAATGATATGTTTGATCCTATTCGGAACAAATCTTTCTCCTTGGATCACATGAATATTTATGATTCCAAGTTTT** GGGAAGAAGCGACACCAATATGGATCACAAACCAGAGGGCAGGACATACTAGTGGTGCAGCCATGTGGCCCGGA ACAGATGTAAAAATACATAAGCGCTTTCCTACTCATTACATGCCTTACAATGAGTCAGTTTCATTTGAAGATAG AGTTGCCAAAATTGTTGAATGGTTTACGTCAAAAGAGCCCATAAATCTTGGTCTTCTCTATTGGGAAGACCCTG ATGACATGGGCCACCATTTGGGACCTGACAGTCCGCTCATGGGGCCTGTCATTTCAGATATTGACAAGAAGTTA GGATATCTCATACAAATGCTGAAAAAGGCAAAGTTGTGGAACACTCTGAACCTAATCATCACAAGTGATCATGG **AATGACGCAGTGCTCTGAGGAAAGGTTAATAGAACTTGACCAGTACCTGGATAAAGACCACTATACCCTGATTG** ATCAATCTCCAGTAGCAGCCATCTTGCCAAAAGAAGGTAAATTTGATGAAGTCTATGAAGCACTAACTCACGCT CATCCTAATCTTACTGTTTACAAAAAAGAAGACGTTCCAGAAAGGTGGCATTACAAATACAACAGTCGAATTCA ACCAATCATAGCAGTGGCTGATGAAGGGTGGCACATTTTACAGAATAAGTCAGATGACTTTCTGTTAGGCAACC TCAAAAGAAGCCATGAACTCCACAGATTTGTACCCACTACTATGCCACCTCCTCAATATCACTGCCATGCCACA CAATGGATCATTCTGGAATGTCCAGGATCTGCTCAATTCAGCAATGCCAAGGGTGGTCCCTTATACACAGAGTA CTATACTCCTCCTGGTAGTGTTAAACCAGCAGAATATGACCAAGAGGGGTCATACCCTTATTTCATAGGGGTC TCTCTTGGCAGCATTATAGTGATTGTATTTTTTGTAATTTCATTAAGCATTTAATTCACAGTCAAATACCTGC $\tt CTTACAAGATATGCATGCTGAAATAGCTCAACCATTATTACAAGCC\underline{ran}_{\tt TGTTACTTTGAAGTGGATTTGCATA$ TTGAAGTGGAGATTCCATAATTATGTCAGTGTTTAAAGGTTTCAAATTCTGGGAAACCAGTTCCAAACATCTGC ATCCTGCTTTATTTGGACTTGGCGCAGATAATGTATATATTTAGCAACTTTGCACTATGTAAAGTACCTTATAT ATTGCACTTTAAATTTCTCTCCTGATGGGTACTTTAATTTGAAATGCACTTTATGGACAGTTATGTCTTATAAC TTGATTGAAAATGACAACTTTTTGCACCCATGTCACAGAATACTTGTTACGCATTGTTCAAACTGAAGGAAATT TCTAATAATCCCGAATAATGAACATAGAAATCTATCTCCATAAATTGAGAGAAGAAGAAGGTGATAAGTGTTGA AAATTAAATGTGATAACCTTTGAACCTTGAATTTTGGAGATGTATTCCCAACAGCAGAATGCAACTGTGGGCAT ATTCGTTCTAAATATTGTTTCTGTCATAAAATTATTGTGATTTCCTGATGAGTCATATTACTGTGATTTTCA TAATAATGAAGACACCATGAATATACTTTTCTTCTATATAGTTCAGCAATGGCCTGAATAGAAGCAACCAGGCA AAATCAAATTGGATAAAAAAAAAAAAAAAAAAA

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FIGURE 202

MTSKFILVSFILAALSLSTTFSLQLDQQKVLLVSFDGFRWDYLYKVPTPHFHYIMKYGVHVK
QVTNVFITKTYPNHYTLVTGLFAENHGIVANDMFDPIRNKSFSLDHMNIYDSKFWEEATPIW
ITNQRAGHTSGAAMWPGTDVKIHKRFPTHYMPYNESVSFEDRVAKIVEWFTSKEPINLGLLY
WEDPDDMGHHLGPDSPLMGPVISDIDKKLGYLIQMLKKAKLWNTLNLIITSDHGMTQCSEER
LIELDQYLDKDHYTLIDQSPVAAILPKEGKFDEVYEALTHAHPNLTVYKKEDVPERWHYKYN
SRIQPIIAVADEGWHILQNKSDDFLLGNHGYDNALADMHPIFLAHGPAFRKNFSKEAMNSTD
LYPLLCHLLNITAMPHNGSFWNVQDLLNSAMPRVVPYTQSTILLPGSVKPAEYDQEGSYPYF
IGVSLGSIIVIVFFVIFIKHLIHSQIPALQDMHAEIAQPLLQA

Signal Peptide:

amino acids 1-22

Transmembrane Domain:

amino acids 429-452

N-glycosylation sites:

amino acids 101-104, 158-161, 292-295, 329-332, 362-365, 369-372, 382-385, 389-392

Somatomedin B Domain:

amino acids 69-85

Sulfatase protein Region:

amino acids 212-241

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FIGURE 203

GGATTTTTGTGATCCGCGATTCGCTCCCACGGGCGGACCTTTGTAACTGCGGGAGGCCCAG AGAGAGGCCAAGCCCCTTGCCTTGGGTCACACAGCCAAAGGAGGCAGAGCCAGAACTCACAA CCAGATCCAGAGGCAACAGGGACATGCCCACCTGGGACGAAAAGGCAGTCACCCGCAGGGCC AAGGTGGCTCCCGCTGAGAGGATGAGCAAGTTCTTAAGGCACTTCACGGTCGTGGGAGACGA AGCAGCCACCACCCACTCTCAGGCGAGGAAGGCAGAGCTGCAGCCCCTGACGTTGCC CCTGCCCTGGCCCCGCACCCAGGGCCCCCTTGACTTCAGGGGCATGTTGAGGAAACTGTT CAGCTCCCACAGGTTTCAGGTCATCATCTGCTTGGTGGTTCTGGATGCCCTCCTGGTGC TTGCTGAGCTCATCCTGGACCTGAAGATCATCCAGCCCGACAAGAATAACTATGCTGCCATG ATTTGTCTTCCGCCTGAGTTCTTTCACCACAAGTTTGAGATCCTGGATGCCCGTCGTGGTGG TGGTCTCATTCATCCTGGACATTGTCCTCCTGTTCCAGGAGCACCAGTTTGAGGCTCTGGGC CTGCTGATTCTGCTCCGGCTGTGGCGGGTGGCCCGGATCATCAATGGGATTATCATCTCAGT TAAGACACGTTCAGAACGGCAACTCTTAAGGTTAAAACAGATGAATGTACAATTGGCCGCCA AGATTCAACACCTTGAGTTCAGCTGCTCTGAGAAGCCCCTGGAC<u>TGA</u>TGAGTTTGCTGTATC AACCTGTAAGGAGAAGCTCTCTCCGGATGGCTATGGGAATGAAAGAATCCGACTTCTACTCT CAGGCTGGCATGTTCACTGGGCTGTTTACGACAGAGAACCTGACAGTCACTGGCCAGTTA TCACTTCAGATTACAAATCACACAGAGCATCTGCCTGTTTTCAATCACAAGAGAACAAAACC AAAATCTATAAAGATATTCTGAAAATATGACAGAATTTGACAAATAAAAGCATAAACGTGTA

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FIGURE 204

MATWDEKAVTRRAKVAPAERMSKFLRHFTVVGDDYHAWNINYKKWENEEEEEEEQPPPTPV SGEEGRAAAPDVAPAPGPAPRAPLDFRGMLRKLFSSHRFQVIIICLVVLDALLVLAELILDL KIIQPDKNNYAAMVFHYMSITILVFFMMEIIFKLFVFRLSSFTTSLRSWMPVVVVVSFILDI VLLFQEHQFEALGLLILLRLWRVARIINGIIISVKTRSERQLLRLKQMNVQLAAKIQHLEFS CSEKPLD

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FIGURE 205

CGGCTCGAGCTCGAGCCGAATCGGCTCGAGGGGCAGTGGAGCACCCAGCAGGCCGCCAAC<u>AT</u> **G**CTCTGTCTGTGCCTGTACGTGCCGGTCATCGGGGAAGCCCAGACCGAGTTCCAGTACTTTG AGTCGAAGGGGCTCCCTGCCGAGCTGAAGTCCATTTTCAAGCTCAGTGTCTTCATCCCCTCC CAGGAATTCTCCACCTACCGCCAGTGGAAGCAGAAAATTGTACAAGCTGGAGATAAGGACCT TGATGGGCAGCTAGACTTTGAAGAATTTGTCCATTATCTCCAAGATCATGAGAAGAAGCTGA GGCTGGTGTTTAAGATTTTGGACAAAAAGAATGATGGACGCATTGACGCGCAGGAGATCATG CATGGATAAAAACGGCACGATGACCATCGACTGGAACGAGTGGAGAGACTACCACCTCCTCC ACCCCGTGGAAAACATCCCCGAGATCATCCTCTACTGGAAGCATTCCACGATCTTTGATGTG GGTGAGAATCTAACGGTCCCGGATGAGTTCACAGTGGAGGAGGCAGACGGGGATGTGGTG GAGACACCTGGTGGCAGGAGGTGGGGCCAGGGGCCCCCCTGG ACAGGCTCAAGGTGCTCATGCAGGTCCATGCCCCCGCAGCAACACATGGGCATCGTTGGT GGCTTCACTCAGATGATTCGAGAAGGAGGGGCCAGGTCACTCTGGCGGGGCAATGGCATCAA CGTCCTCAAAATTGCCCCCGAATCAGCCATCAAATTCATGGCCTATGAGCAGATCAAGCGCC TTGTTGGTAGTGACCAGGAGACTCTGAGGATTCACGAGAGGCTTGTGGCAGGGTCCTTGGCA GGGGCCATCGCCCAGAGCAGCATCTACCCAATGGAGGTCCTGAAGACCCGGATGGCGCTGCG GAAGACAGGCCAGTACTCAGGAATGCTGGACTGCGCCAGGAGGATCCTGGCCAGAGAGGGGG TGGCCGCCTTCTACAAAGGCTATGTCCCCAACATGCTGGGCATCATCCCCTATGCCGGCATC GACCTTGCAGTCTACGAGACGCTCAAGAATGCCTGGCTGCAGCACTATGCAGTGAACAGCGC GGACCCCGGCGTGTTTGTGCTCCTGGCCTGTGGCACCATGTCCAGTACCTGTGGCCAGCTGG CCAGCTACCCCCTGGCCCTAGTCAGGACCCGGATGCAGGCGCAAGCCTCTATTGAGGGCGCT CCGGAGGTGACCATGAGCAGCCTCTTCAAACATATCCTGCGGACCGAGGGGGCCTTCGGGCT GTACAGGGGGCTGGCCCCCAACTTCATGAAGGTCATCCCAGCTGTGAGCATCAGCTACGTGG TCTACGAGAACCTGAAGATCACCCTGGGCGTGCAGTCGCGG<u>TGA</u>CGGGGGGGGGGGCCGCCCG

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FIGURE 206

MLCLCLYVPVIGEAQTEFQYFESKGLPAELKSIFKLSVFIPSQEFSTYRQWKQKIVQAGDKD LDGQLDFEEFVHYLQDHEKKLRLVFKILDKKNDGRIDAQEIMQSLRDLGVKISEQQAEKILK SMDKNGTMTIDWNEWRDYHLLHPVENIPEIILYWKHSTIFDVGENLTVPDEFTVEERQTGMW WRHLVAGGGAGAVSRTCTAPLDRLKVLMQVHASRSNNMGIVGGFTQMIREGGARSLWRGNGI NVLKIAPESAIKFMAYEQIKRLVGSDQETLRIHERLVAGSLAGAIAQSSIYPMEVLKTRMAL RKTGQYSGMLDCARRILAREGVAAFYKGYVPNMLGIIPYAGIDLAVYETLKNAWLQHYAVNS ADPGVFVLLACGTMSSTCGQLASYPLALVRTRMQAQASIEGAPEVTMSSLFKHILRTEGAFG LYRGLAPNFMKVIPAVSISYVVYENLKITLGVQSR

Important features:

Signal peptide:

amino acids 1-16

Transmembrane domain:

amino acids 284-304, 339-360, 376-394

Mitochondrial energy transfer proteins signature.

amino acids 206-215, 300-309

N-glycosylation site.

amino acids 129-133, 169-173

Elongation Factor-hand calcium-binding protein.

amino acids 54-73, 85-104, 121-140

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FIGURE 207

GGAAGGCAGCGCAGCTCCACTCAGCCAGTACCCAGATACGCTGGGAACCTTCCCCAGCCAT CAATTGCACTCATCATTGGCTTTGGTATTTCAGGGAGACACTCCATCACAGTCACTGTC GCCTCAGCTGGGAACATTGGGGAGGATGGAATCCTGAGCTGCACTTTTGAACCTGACATCAA ACTTTCTGATATCGTGATACAATGGCTGAAGGAAGGTGTTTTAGGCTTGGTCCATGAGTTCA AAGAAGGCAAAGATGAGCTGTCGGAGCAGGATGAAATGTTCAGAGGCCGGACAGCAGTGTTT GCTGATCAAGTGATAGTTGGCAATGCCTCTTTGCGGCTGAAAAACGTGCAACTCACAGATGC TGGCACCTACAAATGTTATATCATCACTTCTAAAGGCAAGGGGAATGCTAACCTTGAGTATA AAACTGGAGCCTTCAGCATGCCGGAAGTGAATGTGGACTATAATGCCAGCTCAGAGACCTTG CGGTGTGAGGCTCCCCGATGGTTCCCCCAGCCCACAGTGGTCTGGGCATCCCAAGTTGACCA GGGAGCCAACTTCTCGGAAGTCTCCAATACCAGCTTTGAGCTGAACTCTGAGAATGTGACCA TGAAGGTTGTGTCTGTGCTCTACAATGTTACGATCAACACACATACTCCTGTATGATTGAA AATGACATTGCCAAAGCAACAGGGGATATCAAAGTGACAGAATCGGAGATCAAAAGGCGGAG GGGCACTTCTGCCTCTCAGCCCTTACCTGATGCTAAAATAATGTGCCTTGGCCACAAAAAAG CATGCAAAGTCATTGTTACAACAGGGATCTACAGAACTATTTCACCACCAGATATGACCTAG TTTTATATTTCTGGGAGGAAATGAATTCATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCA GACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAAGAGTGATAAG GGGGAGTGAGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTG TAATGTTGCTCTGAGGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCA CAAATTAAGCTGTAGTATGTACCCTAAGACGCTGCTAATTGACTGCCACTTCGCAACTCAGG GGCGGCTGCATTTTAGTAATGGGTCAAATGATTCACTTTTTATGATGCTTCCAAAGGTGCCT TGGCTTCTCTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATAATTTTAGCATAA ACAGAGCAGTCGGGGACACCGATTTTATAAATAAACTGAGCACCTTCTTTTTAAACAAAAAA

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FIGURE 208

MASLGQILFWSIISIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDI KLSDIVIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTD AGTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWASQVD QGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTESEIKRR SHLQLLNSKASLCVSSFFAISWALLPLSPYLMLK

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FIGURE 209

GAATTTGTAGAAGACAGCGGCGTTGCCATGCCGCGTCTCTGGGGCAGGTGTTGGCTCTGGT GCTGGTGGCCGCTCTGTGGGGTGGCACGCAGCCGCTGCTGAAGCGGGCCTCCGCCGGCCTGC AGCGGGTTCATGAGCCGACCTGGGCCCAGCAGTTGCTACAGGAGATGAAGACCCTCTTCTTG AATACTGAGTACCTGATGCCCTTTCTCCTCAACCAGTGTGGATCCCTTCTCTATTACCTCAC CTTGGCATCGACAGATCTGACCCTGGCTGTGCCCATCTGTAACTCTCTGGCTATCATCTTCA CACTGATTGTTGGGAAGGCCCTTGGAGAAGATATTGGTGGAAAACGTAAGTTAGACTACTGC CTCCCAGAGTGGGTGAGGACACGGCCTTTTCCCATCCTGCCCTTTCCTCTGCAGCTGTTTT GCTTCCTTGTGGCCATCAGAGTTCCCTTCCCCTGGACAGTCTGGAGAAAGACAGAGGCTGGG GTTTGGGAT<u>TGA</u>AGACCAGACCCCATCTGAGCCCTTCCTCCAGCCCTGTACCAGCTCCTACT GGCATGGCTGAGCCCTCCTGATTTCTGCCTATTATCCCAGGAGCAGTTGCTGGCAT GGTGCTCACCGTGATAGGAATTTCACTCTGCATCACAAGCTCAGTGAGTAAGACCCAGGGGC AACAGTCTACCCTTTGAGTGGGCCGAACCCACTTCCAGCTCTGCTGCCTCCAGGAAGCCCCT GGGCCATGAAGTGCTGGCAGTGAGCGGATGGACCTAGCACTTCCCCTCTCTGGCCTTAGCTT CCTCCTCTCTTATGGGGATAACAGCTACCTCATGGATCACAATAAGAGAACAAGAGTGAAAG AGTTTTGTAACCTTCAAGTGCTGTTCAGCTGCGGGGATTTAGCACAGGAGACTCTACGCTCA CCCTCAGCAACCTTTCTGCCCCAGCAGCTCTCTTCCTGCTAACATCTCAGGCTCCCAGCCCA GCCACCATTACTGTGGCCTGATCTGGACTATCATGGTGGCAGGTTCCATGGACTGCAGAACT CCAGCTGCATGGAAAGGGCCAGCTGCAGACTTTGAGCCAGAAATGCAAACGGGAGGCCTCTG GGACTCAGTCAGAGCGCTTTGGCTGAATGAGGGGTGGAACCGAGGGAAGAAGGTGCGTCGGA AAATCCTCACTGCCAGCCCCTCTTAAACAGGTAGAGAGCTGTGAGCCCCAGCCCCACCTGAC

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FIGURE 210

MAASLGQVLALVLVAALWGGTQPLLKRASAGLQRVHEPTWAQQLLQEMKTLFLNTEYLMPFL LNQCGSLLYYLTLASTDLTLAVPICNSLAIIFTLIVGKALGEDIGGKRKLDYCECGTQLCGS RHTCVSSFPEPISPEWVRTRPFPILPFPLQLFCFLVAIRVPFPWTVWRKTEAGVWD

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FIGURE 211

CTTCTGTAGGACAGTCACCAGGCCAGATCCAGAAGCCTCTCTAGGCTCCAGCTTTCTCTGTG GAAGATGACAGCAATTATAGCAGGACCCTGCCAGGCTGTCGAAAAGATTCCGCAATAAAACT TTGCCAGTGGGAAGTACCTAGTGAAACGGCCTAAGATGCCACTTCTCTCATGTCCCAGGCT TGAGGCCCTGTGGTCCCCATCCTTGGGAGAAGTCAGCTCCAGCACCATGAAGGGCATCCTCG TTGCTGGTATCACTGCAGTGCTTGTTGCAGCTGTAGAATCTCTGAGCTGCGTGCAGTGTAAT TCATGGGAAAAATCCTGTGTCAACAGCATTGCCTCTGAATGTCCCTCACATGCCAACACCAG CTGTATCAGCTCCTCAGCCAGCTCCTCTCTAGAGACACCAGTCAGATTATACCAGAATATGT TCTGCTCAGCGGAGAACTGCAGTGAGGAGACACACATTACAGCCTTCACTGTCCACGTGTCT GCTGAAGAACACTTTCATTTTGTAAGCCAGTGCTGCCAAGGAAAGGAATGCAGCAACACCAG CGATGCCCTGGACCCTCCCTGAAGAACGTGTCCAGCAACGCAGAGTGCCCTGCTTGTTATG AATCTAATGGAACTTCCTGTCGTGGGAAGCCCTGGAAATGCTATGAAGAAGAACAGTGTGTC TTTCTAGTTGCAGAACTTAAGAATGACATTGAGTCTAAGAGTCTCGTGCTGAAAGGCTGTTC CAACGTCAGTAACGCCACCTGTCAGTTCCTGTCTGGTGAAAACAAGACTCTTGGAGGAGTCA TCCCACACGTGGGCTCCAAAGCTTCCCTCTACCTCTTGGCCCTTGCCAGCCTCCTTCTTCG GGGACTGCTGCCC<u>TGA</u>GGTCCTGGGGCTGCACTTTGCCCAGCACCCCATTTCTGCTTCTCTG AGGTCCAGAGCACCCCTGCGGTGCTGACACCCTCTTTCCCTGCTCTGCCCCGTTTAACTGC CCAGTAAGTGGGAGTCACAGGTCTCCAGGCAATGCCGACAGCTGCCTTGTTCTTCATTATTA

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FIGURE 212

MKGILVAGITAVLVAAVESLSCVQCNSWEKSCVNSIASECPSHANTSCISSSASSSLETPVR LYQNMFCSAENCSEETHITAFTVHVSAEEHFHFVSQCCQGKECSNTSDALDPPLKNVSSNAE CPACYESNGTSCRGKPWKCYEEEQCVFLVAELKNDIESKSLVLKGCSNVSNATCQFLSGENK TLGGVIFRKFECANVNSLTPTSAPTTSHNVGSKASLYLLALASLLLRGLLP

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FIGURE 213

GGGCTTGCCTCACTGGCCACCCTCCCAACCCCAAGAGCCCAGCCCCATGGTCCCCGCCGCCG ACCCAGACTCCGACCGAAATGCAGCGGGTCAGTTTACGCTTTGGGGGCCCCATGACCCGCAG CTACCGGAGCACCGCCCGGACTGGTCTTCCCCGGAAGACAAGGATAATCCTAGAGGACGAGA ATGATGCCATGGCCGACGCCGACCGCCTGGCTGGACCAGCGGCTGCCGAGCTCTTGGCCGCC ACGGTGTCCACCGGCTTTAGCCGGTCGTCCGCCATTAACGAGGAGGATGGGTCTTCAGAAGA GGGGGTTGTGATTAATGCCGGAAAGGATAGCACCAGCAGAGAGCTTCCCAGTGCGACTCCCA ATACAGCGGGGAGTTCCAGCACGAGGTTTATAGCCAATAGTCAGGAGCCTGAAATCAGGCTG ACTTCAAGCCTGCCGCGCTCCCCGGGAGGTCTACTGAGGACCTGCCAGGCTCGCAGGCCAC CCTGAGCCAGTGGTCCACACCTGGGTCTACCCCGAGCCGGTGGCCGTCACCCTCACCCACAG CCATGCCATCTCCTGAGGATCTGCGGCTGGTGCTGATGCCCTGGGGCCCGTGGCACTGCCAC TGCAAGTCGGGCACCATGAGCCGGAGCCGGTCTGGGAAGCTGCACGGCCTTTCCGGGCGCCCT TCGAGTTGGGGCGCTGAGCCAGCTCCGCACGGAGCACAAGCCTTGCACCTATCAACAATGTC CCTGCAACCGACTTCGGGAAGAGTGCCCCCTGGACAAGTCTCTGTACTGACACCAACTGT GCCTCTCAGAGCACCACTACCAGGACCACCACTACCCCCTTCCCCACCATCCACCTCAG AAGCAGTCCCAGCCTGCCACCCGCCAGCCCTGCCCAGCCTTTTTTGGAAACGGGTCA GGATTGGCCTGGAGGATATTTGGAATAGCCTCTCTTCAGTGTTCACAGAGATGCAACCAATA GACAGAAACCAGAGGTAATGGCCACTTCATCCACATGAGGAGATGTCAGTATCTCAACCTCT CTTGCCCTTTCAATCCTAGCACCCACTAGATATTTTTAGTACAGAAAAACAAAACTGGAAAA CACAA

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FIGURE 214

MVPAAGALLWVLLLNLGPRAAGAQGLTQTPTEMQRVSLRFGGPMTRSYRSTARTGLPRKTRI
ILEDENDAMADADRLAGPAAAELLAATVSTGFSRSSAINEEDGSSEEGVVINAGKDSTSREL
PSATPNTAGSSSTRFIANSQEPEIRLTSSLPRSPGRSTEDLPGSQATLSQWSTPGSTPSRWP
SPSPTAMPSPEDLRLVLMPWGPWHCHCKSGTMSRSRSGKLHGLSGRLRVGALSQLRTEHKPC
TYQQCPCNRLREECPLDTSLCTDTNCASQSTTSTRTTTTPFPTIHLRSSPSLPPASPCPALA
FWKRVRIGLEDIWNSLSSVFTEMQPIDRNQR

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FIGURE 215

GCGGCGCTGGCGAGCGGCTCCCAGGGCGACCGTGAGCCGGTGTACCGCGACTGCGTACTGCAGTGCGAAGAGCA GTCGGGACGACTGTAAGTATGAGTGTATGTGGGTCACCGTTGGGCTCTACCTCCAGGAAGGTCACAAAGTGCCT CAGTTCCATGGCAAGTGGCCCTTCTCCCGGTTCCTGTTCTTTCAAGAGCCGGCATCGGCCGTGGCCTCGTTTCT CAATGGCCTGGCCAGCCTGGTGATGCTCTGCCGCTACCGCACCTTCGTGCCAGCCTCCTCCCCCATGTACCACA CCTGTGTGGCCTTCGCCTGGGTGTCCCTCAATGCATGGTTCTGGTCCACAGTCTTCCACACCAGGGACACTGAC CTCACAGAGAAAATGGACTACTTCTGTGCCTCCACTGTCATCCTACACTCAATCTACCTGTGCTGCGTCAGGAC CGTGGGGCTGCAGCACCCAGCTGTGGTCAGTGCCTTCCGGGCTCTCCTGCTGCTCATGCTGACCGTGCACGTCT CCTACCTGAGCCTCATCCGCTTCGACTATGGCTACAACCTGGTGGCCAACGTGGCTATTGGCCTGGTCAACGTG GTGTGGTGGCTGGCCTGTGGAACCAGCGGCGGCTGCCTCACGTGCGCAAGTGCGTGGTGGTGGTCTT GCTGCTGCAGGGGCTGTCCCTGCTCGAGCTGCTTGACTTCCCACCGCTCTTCTGGGTCCTGGATGCCCATGCCA TCTGGCACATCAGCACCATCCCTGTCCACGTCCTTTTTCAGCTTTCTGGAAGATGACAGCCTGTACCTGCTG AAGGAATCAGAGGACAAGTTCAAGCTGGAC<u>TGA</u>AGACCTTGGAGCGAGTCTGCCCCAGTGGGGGATCCTGCCCCC GCCCTGCTGGCCTCCCCTCAACCCTTGAGATGATTTTCTCTTTTCAACTTCTTGAACTTGGACATGA AGGATGTGGCCCAGAATCATGTGGCCAGCCCACCCCTGTTGGCCCTCACCAGCCTTGGAGTCTGTTCTAGGG AAGGCCTCCCAGCATCTGGGACTCGAGAGTGGGCAGCCCCTCTACCTCCTGGAGCTGAACTGGGGTGGAACTGA GTGTGTTCTTAGCTCTACCGGGAGGACAGCTGCCTGTTTCCTCCCCACCAGCCTCCTCCCCACATCCCCAGCTG ${\tt CCTGGCTGGGTCCTGAAGCCCTCTGTCTACCTGGGAGACCAGGGACCACAGGCCTTAGGGATACAGGGGGTCCC}$ GGTTCACGGCGATTCTCCCCATGGGATCTTGAGGGACCAAGCTGCTGGGATTGGGAAGGAGTTTCACCCTGACC GTTGCCCTAGCCAGGTTCCCAGGAGGCCTCACCATACTCCCTTTCAGGGCCAGGGCTCCAGCAAGCCCAGGGCA AGGATCCTGTGCTGCTGTTGAGAGCCTGCCACCGTGTGTCGGGAGTGTGGGCCAGGCTGAGTGCATAGG TGACAGGGCCGTGAGCATGGGCCTGGGTGTGTGTGAGCTCAGGCCTAGGTGCGCAGTGTGGAGACGGGTGTTGT TGCGCGTGCTGGTGGGCATGTGAGATGAGTGACTGCCGGTGAATGTGTCCACAGTTGAGAGGTTGGAGCAGGAT GAGGGAATCCTGTCACCATCAATAATCACTTGTGGAGCGCCAGCTCTGCCCAAGACGCCACCTGGGCGGACAGC CAGGAGCTCTCCATGGCCAGGCTGCCTGTGTGCATGTTCCCTGTCTGGTGCCCCTTTGCCCGCCTCCTGCAAAC CTCACAGGGTCCCCACACACAGTGCCCTCCAGAAGCAGCCCCTCGGAGGCAGAGGAAAAATGGGGATGGC GCTGCCAGCCCTTTGCCATAGCCTGATTTTGGGGAGGAGGAGGGGGCGATTTGAGGGAGAAGGGGAGAAAGCT ACACTATGCCTGTGCCCTGGTAAAGGTGACCCCTGCCATTTACCAGCAGCCCTGGCATGTTCCTGCCCCACAGG AATAGAATGGAGGGAGCTCCAGAAACTTTCCATCCCAAAGGCAGTCTCCGTGGTTGAAGCAGACTGGATTTTTG GCCTGCGCTAGCTTCTTTTGATACTGAAAACTTTTAAGGTGGGAGGGTGGCAAGGGATGTGCTTAATAAATCAA TTCCAAGCCTCAAAAAAAAAAAAAAAA

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FIGURE 216

MAGLAARLVLLAGAAALASGSQGDREPVYRDCVLQCEEQNCSGGALNHFRSRQPIYMSLAGW
TCRDDCKYECMWVTVGLYLQEGHKVPQFHGKWPFSRFLFFQEPASAVASFLNGLASLVMLCR
YRTFVPASSPMYHTCVAFAWVSLNAWFWSTVFHTRDTDLTEKMDYFCASTVILHSIYLCCVR
TVGLQHPAVVSAFRALLLLMLTVHVSYLSLIRFDYGYNLVANVAIGLVNVVWWLAWCLWNQR
RLPHVRKCVVVVLLLQGLSLLELLDFPPLFWVLDAHAIWHISTIPVHVLFFSFLEDDSLYLL
KESEDKFKLD

Important features:

Signal peptide:

amino acids 1-20

Transmembrane domains:

amino acids 105-123, 138-156, 169-185, 193-209, 221-240, 256-272

N-glycosylation site.

amino acids 40-44

N-myristoylation site.

amino acids 43-49

CUB domain proteins profile.

amino acids 285-302

Amiloride-sensitive sodium channels proteins.

amino acids 162-186

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FIGURE 217

GGCCGCCTGGAATTGTGGGAGTTGTGTCTGCCACTCGGCTGCCGGAGGCCGAAGGTCCGTGA CTATGCTCCCCAGAGCCTGCCTTCATCTAGGATGCCTCCTCTGGGCATGCTGCTTGGGCTG CTGATGGCCGCCTGCTTCACCTTCTGCCTCAGTCATCAGAACCTGAAGGAGTTTGCCCTGAC TGGATGCCGAAGTCCTGGAGGTGTTCCACCCGACGCATGAGTGGCAGGCCCTTCAGCCAGGG CAGGCTGTCCCTGCAGGATCCCACGTACGGCTGAATCTTCAGACTGGGGAAAGAGAGGCCAAA ACTCCAATATGAGGACAAGTTCCGAAATAATTTGAAAGGCAAAAGGCTGGATATCAACACCA ACACCTACACATCTCAGGATCTCAAGAGTGCACTGGCAAAATTCAAGGAGGGGGCAGAGATG GAGAGTTCAAAGGAAGACAAGGCAAGGCAGGCTGAGGTAAAGCGGCTCTTCCGCCCCATTGA GGAACTGAAGAAGACTTTGATGAGCTGAATGTTGTCATTGAGACTGACATGCAGATCATGG TACGGCTGATCAACAAGTTCAATAGTTCCAGCTCCAGTTTGGAAGAGAAGATTGCTGCGCTC TTTGATCTTGAATATTATGTCCATCAGATGGACAATGCGCAGGACCTGCTTTCCTTTGGTGG TCTTCAAGTGGTGATCAATGGGCTGAACAGCACAGAGCCCCTCGTGAAGGAGTATGCTGCGT TTGTGCTGGGCGCTGCCTTTTCCAGCAACCCCAAGGTCCAGGTGGAGGCCATCGAAGGGGGA GCCCTGCAGAAGCTGCTGGTCATCCTGGCCACGGAGCAGCCGCTCACTGCAAAGAAGAAGGT CCTGTTTGCACTGTGCTCCCTGCTGCGCCACTTCCCCTATGCCCAGCGGCAGTTCCTGAAGC TCGGGGGGCTGCAGGTCCTGAGGACCCTGGTGCAGGAGAAGGGCACGGAGGTGCTCGCCGTG CGCGTGGTCACACTGCTCTACGACCTGGTCACGAGAAGATGTTCGCCGAGGAGGAGGCTGA GCTGACCCAGGAGATGTCCCCAGAGAAGCTGCAGCAGTATCGCCAGGTACACCTCCTGCCAG GCCTGTGGGAACAGGGCTGGTGCGAGATCACGGCCCACCTCCTGGCGCTGCCCGAGCATGAT GCCCGTGAGAAGGTGCTGCAGACACTGGGCGTCCTCCTGACCACCTGCCGGGACCGCTACCG TCAGGACCCCCAGCTCGGCAGGACACTGGCCAGCCTGCAGGCTGAGTACCAGGTGCTGGCCA GCCTGGAGCTGCAGGATGGTGAGGACGAGGGCTACTTCCAGGAGCTGCTGGGCTCTGTCAAC AGCTTGCTGAAGGAGCTGAGATGAGGCCCCACACCAGGACTGGACTGGGATGCCGCTAGTGA GGCTGAGGGTGCCAGCGTGGGTGGGCTTCTCAGGCAGGAGGACATCTTGGCAGTGCTGGCT

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FIGURE 218

MAPQSLPSSRMAPLGMLLGLLMAACFTFCLSHQNLKEFALTNPEKSSTKETERKETKAEEEL
DAEVLEVFHPTHEWQALQPGQAVPAGSHVRLNLQTGEREAKLQYEDKFRNNLKGKRLDINTN
TYTSQDLKSALAKFKEGAEMESSKEDKARQAEVKRLFRPIEELKKDFDELNVVIETDMQIMV
RLINKFNSSSSSLEEKIAALFDLEYYVHQMDNAQDLLSFGGLQVVINGLNSTEPLVKEYAAF
VLGAAFSSNPKVQVEAIEGGALQKLLVILATEQPLTAKKKVLFALCSLLRHFPYAQRQFLKL
GGLQVLRTLVQEKGTEVLAVRVVTLLYDLVTEKMFAEEEAELTQEMSPEKLQQYRQVHLLPG
LWEQGWCEITAHLLALPEHDAREKVLQTLGVLLTTCRDRYRQDPQLGRTLASLQAEYQVLAS
LELQDGEDEGYFQELLGSVNSLLKELR

Important features:

Signal peptide:

amino acids 1-29

Hypothetical YJL126w/YLR351c/yhcX family protein.

amino acids 364-373

N-glycosylation site.

amino acids 193-197, 236-240

N-myristoylation site.

amino acids 15-21, 19-25, 234-240, 251-257, 402-408, 451-457

Homologous region SLS1 protein.

amino acids 68-340

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FIGURE 219

TTCGGCTTCCGTAGAGGAAGTGGCGCGGACCTTCATTTGGGGTTTCGGTTCCCCCCCTTCCC CTTCCCCGGGGTCTGGGGGTGACATTGCACCGCGCCCCTCGTGGGGTCGCGTTGCCACCCCA CGCGGACTCCCAGCTGGCGCGCCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCC TTCCCACCTGACCAGCCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTCGCGTTCGGC CCGGCCTTCGCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGT CGCAGGGGCATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGG TCCATGTGACCGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCT GTCTCTGTCCTTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGA TGAAGGGTTAGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCT ATGTTTCTGGTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCT GATGCACTTGGGCCAGGTGTGGTTGGGATCCATGGAGACTCACCCTATTACTTCCTGACTTC AGCCTTTCTGACAGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATG CCTGTGAGAGGGGGCTTGGGCCTTGGGCCTGGTGGTTGGGAGTCACCTACTGACATCG GGACTGACATTCCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCCATCTATGCAGTCACTGT TTCCATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCTCCGAAGTATTCAGCGCAGCC CCCATGACTGAGCCCAGCCCGGGTCCATTGCCCACATTCTCTGTCTCCTTCTCGTC GGTCTACCCCACTACCTCCAGGGTTTTGCTTTGTCCTTTTGTGACCGTTAGTCTCTAAGCTT TACCAGGAGCAGCCTGGGTTCAGCCAGTCAGTGACTGGTTGGATTTGAATCTGCACTTATCCC CACCACCTGGGGACCCCCTTGTTGTGTCCAGGACTCCCCCTGTGTCAGTGCTCTGCTCTCAC CCTGCCCAAGACTCACCTCCCTTCCCCTCTGCAGGCCGACGGCAGGAGACAGTCGGGTGAT GGTGTATTCTGCCCTGCGCATCCCACCCGAGGACTGAGGGAACCTAGGGGGGACCCCTGGGC CTGGGGTGCCCTCGTGATGTCCTCGCCCTGTATTTCTCCATCTCCAGTTCTGGACAGTGCAG GTTGCCAAGAAAAGGGACCTAGTTTAGCCATTGCCCTGGAGATGAAATTAATGGAGGCTCAA GGATAGATGAGCTCTGAGTTTCTCAGTACTCCCTCAAGACTGGACATCTTGGTCTTTTTCTC GAGGTGGGGGGGGGGGGGGTATATTGGAACTCTTCTAACCTCCTTGGGCTATATTTTCTC TCCTCGAGTTGCTCCTCATGGCTGGGCTCATTTCGGTCCCTTTCTCCTTGGTCCCAGACCTT GGGGGAAAGGAAGTGCATGTTTGGGAACTGCATTACTGGAACTAATGGTTTTAACCT CCTTAACCACCAGCATCCCTCCTCTCCCCAAGGTGAAGTGGAGGGTGCTGTGGTGAGCTGGC CACTCCAGAGCTGCAGTGCCACTGGAGGAGTCAGACTACCATGACATCGTAGGGAAGGAGGG ATCATTTTCTGCTGAGGGTGGAGTGTCCCATCCTTTTAATCAAGGTGATTGTGATTTTGACT ΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑ

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FIGURE 220

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILVHVTDR SDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYVSGLS FGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTFWGVVFFDACERRR YWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQRSLLCKD

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FIGURE 221

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FIGURE 222

GACCGACCGTTCAGATGCCCGGTTCCAGTACGGCTTCCTGATTTTTGGTGCTGCTGTNTCTG
TCCTTCTACAGGAGGTGTTCCGCTTTGCCTANTACAAGCTGCTTAAGAAGGCAGATGAGGGG
TTAGCATNGCTGAGTGAGGACGGAAGATCACCCATTTCCATCCGCCAGATGGCCTATGTTTN
TGGTNTTTCCTTCGGTATCATCAGTGGTGTTTTNTCTGTTATCAATATTTTGGNTGATGCAN
TTGGGCCAGGTGTGGTTGGGATCCATGGAGANTCACCCTATTAATTCCTGAATTCAGCCTTT
NTGACAGCAGCCATTATCCTGNTCCATACCTTTTGGGGAGTTGTGTTTTTTTGATGCCTGTGA
GAGGAG

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FIGURE 223

NGTTGGAGAAGTGGCGCGGACNTTCATTTGGGGTTTCCCCCCTTTCCCCTTTCCCCG
GGGTCTGGGGTGACATTGCACGGGCCCCTCGTGGGGTCGCGTTGCCACCCCACGCGGACTCC
CCAGNTGGNGCGCCCTTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCCTTCCCACNTG
ACCAGCCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTCGCGTTCGGCCCGGCCTTCG
CGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTCGCAGGGGCA
TTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGTTCATCTTTGGTCCATGTGAC
CGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCTTCTCTCC
TTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGATGAGGGGTTA
GCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTGG
TCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTTGGCTGATGCACTTG
GGCCAGGTGTGGTTGGGATCCATGGAGACTCACCC

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FIGURE 224

GTAAAAGAAAGTGGCCGGACCTTCATTGGGGTTTCGGTTCCCCCCTTTCCCNTTCCCGGGG
TCTGGGGGTGACATTGCACCGCGCCCNTCGTGGGGTCGCGTTGCCACCCCACGCGGACTCCC
CAGNTGGCGCGCCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCCTTCCCACCTGA
CCAGCCATGGGGGCTGCGGTGTTTTTCGGGCTGCACTTTCGTCGCGTTCGGGCCCGGCCTTC
GCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTCGCAGGGGC
ATTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGTTCATCTTGGTCCATGTGA
CCGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTC
CTTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGATGAGGGGTT
AGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTG
GTCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTT
GGGCCAGGTGTGGTTTGGGATCCATGGAGAC

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FIGURE 225

GCCCCAGGGAGCAGTGGTGTTATAACTCAGGCCCGGTGCCCAGAGCCCAGGAGGAGGAGGCAG TGGCCAGGAAGGCACAGGCCTGAGAAGTCTGCGGCTGAGCTGGGAGCAAATCCCCCACCCCC TGTCTGTGCGTCCTGCACCCACATCTTTCTCTGTCCCCTTGCCCTGTCTGGAGGCTGCT AGACTCCTATCTTCTGAATTCTATAGTGCCTGGGTCTCAGCGCAGTGCCGATGGTGGCCCGT CCTTGTGGTTCCTCTACCTGGGGAAATAAGGTGCAGCGGCC<u>ATG</u>GCTACAGCAAGACCCC CCTGGATGTGGGTGCTCTGTGCTCTGATCACAGCCTTGCTTCTGGGGGTCACAGAGCATGTT CTCGCCAACATGATGTTTCCTGTGACCACCCTCTAACACCGTGCCCTCTGGGAGCAACCA GGACCTGGGAGCTGGGGCCGGGGAAGACGCCCGGTCGGATGACAGCAGCCGCATCATCA ATGGATCCGACTGCGATATGCACACCCAGCCGTGGCAGGCCGCGCTGTTGCTAAGGCCCAAC CAGCTCTACTGCGGGGCGGTGTTGGTGCATCCACAGTGGCTGCTCACGGCCGCCCACTGCAG GAAGAAAGTTTTCAGAGTCCGTCTCGGCCACTACTCCCTGTCACCAGTTTATGAATCTGGGC AGCAGATGTTCCAGGGGGTCAAATCCATCCCCCACCCTGGCTACTCCCACCCTGGCCACTCT AACGACCTCATGCTCATCAAACTGAACAGAAGAATTCGTCCCACTAAAGATGTCAGACCCAT CCAAGAGCCCCCAAGTGCACTTCCCTAAGGTCCTCCAGTGCTTGAATATCAGCGTGCTAAGT CAGAAAAGGTGCGAGGATGCTTACCCGAGACAGATAGATGACACCATGTTCTGCGCCGGTGA CAAAGCAGGTAGAGACTCCTGCCAGGGTGATTCTGGGGGGCCTGTGGTCTGCAATGGCTCCC TGCAGGGACTCGTGTCCTGGGGAGATTACCCTTGTGCCCGGCCCAACAGACCGGGTGTCTAC ACGAACCTCTGCAAGTTCACCAAGTGGATCCAGGAAACCATCCAGGCCAACTCC**TGA**GTCAT CCCAGGACTCAGCACCCGCATCCCCACCTGCTGCAGGGACAGCCCTGACACTCCTTTCAG ACCCTCATTCCTTCCCAGAGATGTTGAGAATGTTCATCTCCAGCCCCTGACCCCATGTCT CCTGGACTCAGGGTCTGCTTCCCCCACATTGGGCTGACCGTGTCTCTCTAGTTGAACCCTGG GAACAATTTCCAAAACTGTCCAGGGCGGGGTTGCGTCTCAATCTCCCTGGGGCACTTTCAT CCTCAAGCTCAGGGCCCATCCCTTCTCTGCAGCTCTGACCCAAATTTAGTCCCAGAAATAAA CTGAGAAGTGGAAAAAAAA

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FIGURE 226

MATARPPWMWVLCALITALLLGVTEHVLANNDVSCDHPSNTVPSGSNQDLGAGAGEDARSDD SSSRIINGSDCDMHTQPWQAALLLRPNQLYCGAVLVHPQWLLTAAHCRKKVFRVRLGHYSLS PVYESGQQMFQGVKSIPHPGYSHPGHSNDLMLIKLNRRIRPTKDVRPINVSSHCPSAGTKCL VSGWGTTKSPQVHFPKVLQCLNISVLSQKRCEDAYPRQIDDTMFCAGDKAGRDSCQGDSGGP VVCNGSLQGLVSWGDYPCARPNRPGVYTNLCKFTKWIQETIQANS

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FIGURE 227

<u>ATCGTCAACGACCGGTGGAAGACCATGGGCGGCGCTGCCCAACTTGAGGACCGGCCGCGCGA</u> CAAGCCGCAGCGGCCGAGCTGCGGCTACGTGCTGCACCGTGCTGCCCTGGCCTGTGC TGCTGGCTGTAGCTGTCACCGGTGCCGTGCTCTTCCTGAACCACGCCCACGCGCCGGGCACG GCGCCCCACCTGTCGTCAGCACTGGGGCTGCCAGCGCCAACAGCGCCCTGGTCACTGTGGA AAGGGCGGACAGCTCGCACCTCAGCATCCTCATTGACCCGCGCTGCCCCGACCTCACCGACA GCTTCGCACGCCTGGAGAGCGCCCAGGCCTCGGTGCTGCAGGCGCTGACAGAGCACCAGGCC ACGGCTCCGTGAACTTCTTCCGGGGCTGGGACGCTGGACGGCTTTTGGCAGGCTCACC GGGGAGCACTGGCTAGGGCTCAAGAGGATCCACGCCCTGACCACACAGGCTGCCTACGAGCT GCACGTGGACCTGGAGGACTTTGAGAATGGCACGGCCTATGCCCGCTACGGGAGCTTCGGCG TGGGCTTGTTCTCCGTGGACCCTGAGGAAGACGGGTACCCGCTCACCGTGGCTGACTATTCC GGCACTGCAGGCGACTCCCTGAGGACGACGGGCATGAGGTTCACCACCAAGGACCGTGA CAGCGACCATTCAGAGAACAACTGTGCCGCCTTCTACCGCGGTGCCTGGTGGTACCGCAACT GCCACACGTCCAACCTCAATGGGCAGTACCTGCGCGGTGCGCACGCCTCCTATGCCGACGGC GTGGAGTGGTCCTCCTGGACCGCTGGCAGTACTCACTCAAGTTCTCTGAGATGAAGATCCG GCCGGTCCGGGAGGACCGC**TAG**ACTGGTGCACCTTGTCCTTGGCCCTGCTGGTCCCTGTCGC TGCTGTTTGCCGTCCCCTGGCCAGGATGGTGGAGTCTGCCCCAGGCACCCTCTGCCCCCGGCCAAATACCCGGCATTATGGGGACAGAGAGCAGGGGGGCAGACAGCACCCCTGGAGTCCTCCCAGGCAGATCGTGGGGAATGTCAGGTCTCTCTGAGGTCAGGTCTGAGGCCAGTATCCTCCAGCCCCCCAATGCCAACCCCCACCCCGTTTCCCTGGTGCCCAGAGAACCCACCTCTCCCCCAA TGTCCCAGTGCCACCAGGTCATCCACATGCGCAG

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FIGURE 228

MVNDRWKTMGGAAQLEDRPRDKPQRPSCGYVLCTVLLALAVLLAVAVTGAVLFLNHAHAPGT
APPPVVSTGAASANSALVTVERADSSHLSILIDPRCPDLTDSFARLESAQASVLQALTEHQA
QPRLVGDQEQELLDTLADQLPRLLARASELQTECMGLRKGHGTLGQGLSALQSEQGRLIQLL
SESQGHMAHLVNSVSDILDALQRDRGLGRPRNKADLQRAPARGTRPRGCATGSRPRDCLDVL
LSGQQDDGVYSVFPTHYPAGFQVYCDMRTDGGGWTVFQRREDGSVNFFRGWDAYRDGFGRLT
GEHWLGLKRIHALTTQAAYELHVDLEDFENGTAYARYGSFGVGLFSVDPEEDGYPLTVADYS
GTAGDSLLKHSGMRFTTKDRDSDHSENNCAAFYRGAWWYRNCHTSNLNGQYLRGAHASYADG
VEWSSWTGWOYSLKFSEMKIRPVREDR

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FIGURE 229

GCAGTCAGAGACTTCCCCTGCCCCTCGCTGGGAAAGAACATTAGGAATGCCTTTTAGTGCCT TGCTTCCTGAACTAGCTCACAGTAGCCCGGCGGCCCAGGGCAATCCGACCACATTTCACTCT CACCGCTGTAGGAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGCTGGATGATG ATGGGGACACCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACTCGGCATCCAGAGCCC CGGCGCACAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGACCCTGCTGAC TTTGTGCTTGGTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTCAGTACTACC CAAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTCTGCAGCATGTGGC TGAAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGCACACAGGTGCAGCCCTTGTACAG AACAATGGAAATGGCATGGAGACAATTGCTACCAGTTCTATAAAGACAGCAAAAGTTGGGAG CCTGGAATTTGCCGCGTCTCAGAGCTACTCTGAGTTTTTCTACTCTTATTGGACAGGGCTTT TTCCATATTATAATAGATGTCACCAGCCCAAGAAGCAGAGACTGTGTGGCCATCCTCAATGG GATGATCTTCTCAAAGGACTGCAAAGAATTGAAGCGTTGTGTCTGTGAGAAAGGGCAGGAA TGGTGAAGCCAGAGAGCCTCCATGTCCCCCCTGAAACATTAGGCGAAGGTGACTGATTCGCC CTCTGCAACTACAAATAGCAGAGTGAGCCAGGCGGTGCCAAAGCAAGGGCTAGTTGAGACAT TGGGAAATGGAACATAATCAGGAAAGACTATCTCTCTGACTAGTACAAAATGGGTTCTCGTG TTTCCTGTTCAGGATCACCAGCATTTCTGAGCTTGGGTTTATGCACGTATTTAACAGTCACA AGAAGTCTTATTTACATGCCACCAACCAACCTCAGAAACCCATAATGTCATCTGCCTTCTTG GCTTAGAGATAACTTTTAGCTCTCTTTCTTCTCAATGTCTAATATCACCTCCCTGTTTTCAT GTCTTCCTTACACTTGGTGGAATAAGAAACTTTTTGAAGTAGAGGAAATACATTGAGGTAAC ATCCTTTTCTCTGACAGTCAAGTAGTCCATCAGAAATTGGCAGTCACTTCCCAGATTGTACC AGCAAATACACAAGGAATTCTTTTTGTTTGTTTCAGTTCATACTAGTCCCTTCCCAATCCAT CAGTAAAGACCCCATCTGCCTTGTCCATGCCGTTTCCCAACAGGGATGTCACTTGATATGAG AATCTCAAATCTCAATGCCTTATAAGCATTCCTTCCTGTGTCCATTAAGACTCTGATAATTG TCTCCCCTCCATAGGAATTTCTCCCAGGAAAGAAATATATCCCCATCTCCGTTTCATATCAG AACTACCGTCCCCGATATTCCCTTCAGAGAGATTAAAGACCAGAAAAAAGTGAGCCTCTTCA TCTGCACCTGTAATAGTTTCAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTCAG GTACTGAAGATTTAATAATAATAAATGTAAATACTGTGAAAAA

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FIGURE 230

MQAKYSSTRDMLDDDGDTTMSLHSQASATTRHPEPRRTEHRAPSSTWRPVALTLLTLCLVLL
IGLAALGLLFFQYYQLSNTGQDTISQMEERLGNTSQELQSLQVQNIKLAGSLQHVAEKLCRE
LYNKAGAHRCSPCTEQWKWHGDNCYQFYKDSKSWEDCKYFCLSENSTMLKINKQEDLEFAAS
QSYSEFFYSYWTGLLRPDSGKAWLWMDGTPFTSELFHIIIDVTSPRSRDCVAILNGMIFSKD
CKELKRCVCERRAGMVKPESLHVPPETLGEGD

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FIGURE 231

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FIGURE 232

·GCCGAGCGCAAGAACCCTGCGCAGCCCAGAGCAGCTGCTGGAGGGGAATCGAGGCGCGGCTC CCCGAGCCCTCCGGATCCGCCCCCTCCCGGTCCCGCCCCCTCGGAGACTCCTCTGGCTGCT CTGGGGGTTCGCCGGGGCCGGGGACCCGCGGTCCGGGCGCCATGCGGGCATCGCTGCTG TCGGTGCTGCGCCCGCAGGGCCCGTGGCCGTGGGCATCTCCCTGGGCCTTCACCCTGAGCCT AGCTGCCGCCGCGCGAACACCAACGCGGCGCGCCCCAACTCGGTGCAGCCCGGAGCG GAGCGCGAGAAGCCCGGGGCCGGCGAAGGCGCCGGGGAGAATTGGGAGCCGCGCGTCTTGCC CTACCACCTGCACAGCCCGGCCAGGCCGCCAAAAAGGCCGTCAGGACCCGCTACATCAGCA CGGAGCTGGCCATCAGGCAGAGGCTGCTGGTGGCGGTGCTGACCTCTCAGACCACGCTGCCC ACGCTGGGCGTGGCCGTGAACCGCACGCTGGGGCACCGGCTGGAGCGTGTGGTGTTCCTGAC GGGCGCACGGGCCCCGGGCCCCACCTGGCATGGCAGTGGTGACGCTGGGCGAGGAGCGAC CCATTGGACACCTGCACCTGGCGCGCCACCTGCTGGAGCAGCACGGCGACGACTTTGAC TGGTTCTTCCTGGTGCCTGACACCACCTACACCGAGGCGCACGGCCTGGCACGCCTAACTGG GAGAGCCCACCCCGGCCGCTACTGCCACGGAGGCTTTGGGGTGCTGCTGTCGCGCATGCTG CTGCAACAACTGCGCCCCCACCTGGAAGGCTGCCGCAACGACATCGTCAGTGCGCGCCCTGA CGAGTGGCTGGGTCGCATTCTCGATGCCACCGGGGTGGGCTGCACTGGTGACCACGAGG GGGTGCACTATAGCCATCTGGAGCTGAGCCCTGGGGAGCCAGTGCAGGAGGGGGACCCTCAT TTCCGAAGTGCCCTGACAGCCCACCCTGTGCGTGACCCTGTGCACATGTACCAGCTGCACAA AGCTTTCGCCCGAGCTGAACTGGAACGCACGTACCAGGAGATCCAGGAGTTACAGTGGGAGA TCCAGAATACCAGCCATCTGGCCGTTGATGGGGGACCGGGCAGCTGCTTGGCCCGTGGGTATT CCAGCACCATCCCGCCCGGCCTCTCGAGGTGCTGCGCTGGGACTACTTCACGGAGCA GCACGCTTTCTCCTGCGCCGATGGCTCACCCCGCTGCCCACTGCGTGGGGCTGACCGGGCTG ATGTGGCCGATGTTCTGGGGACAGCTCTAGAGGAGCTGAACCGCCGCTACCACCCGGCCTTG CGGCTCCAGAAGCAGCTGGTGAATGGCTACCGACGCTTTGATCCGGCCCGGGGTATGGA ATACACGCTGGACTTGCAGCTGGAGGCACTGACCCCCCAGGGAGGCCGCCGGCCCCTCACTC GCCGAGTGCAGCTCCGGCCGCTGAGCCGCGTGGAGATCTTGCCTGTGCCCTATGTCACT GAGGCCTCACGTCTCACTGTGCTGCTGCCTCTAGCTGCGGCTGAGCGTGACCTGGCCCCTGG CTTCTTGGAGGCCTTTGCCACTGCAGCACTGGAGCCTGGTGATGCTGCGGCAGCCCTGACCC TGCTGCTACTGTATGAGCCGCGCCAGGCCCAGCGCGTGGCCCATGCAGATGTCTTCGCACCT GTCAAGGCCCACGTGGCAGAGCTGGAGCGGCGTTTCCCCGGTGCCCGGGTGCCATGGCTCAG TGTGCAGACAGCCGCACCCTCACCACTGCGCCTCATGGATCTACTCTCCAAGAAGCACCCGC TGGACACACTGTTCCTGCTGGCCGGCCAGACACGGTGCTCACGCCTGACTTCCTGAACCGC TGCCGCATGCATGCCATCTCCGGCTGGCAGGCCTTCTTTCCCATGCATTTCCAAGCCTTCCA CCCAGGTGTGGCCCCACACAGGGCCTGGGCCCCAGAGCTGGGCCGTGACACTGGCCGCT TTGATCGCCAGGCAGCCAGCGAGGCCTGCTTCTACAACTCCGACTACGTGGCAGCCCGTGGG CGCCTGGCGGCAGCCTCAGAACAAGAAGAGGGGCTGCTGGAGAGCCTGGATGTGTACGAGCT ACCGGGCCCAGACGTGCAGCGCGAGGCTCAGTGAGGACCTGTACCACCGCTGCCTCCAGAGC GTGCTTGAGGGCCTCGGCTCCCGAACCCAGCTGGCCATGCTACTCTTTGAACAGGAGCAGGG CAACAGCACCTGACCCCTGTCCCCGTGGGCCGTGGCATGGCCACACCCCACCCCACTT CTCCCCAAAACCAGAGCCACCTGCCAGCCTCGCTGGGCAGGGCTGGCCGTAGCCAGACCCC AAGCTGGCCCACTGGTCCCCTCTCTGGCTCTGTGGGTCCCTGGGCTCTGGACAAGCACTGGG GGACGTGCCCCAGAGCCACCCACTTCTCATCCCAAACCCAGTTTCCCTGCCCCCTGACGCT GCTGATTCGGGCTGTGGCCTCCACGTATTTATGCAGTACAGTCTGCCTGACGCCAGCCCTGC CTCTGGGCCCTGGGGCTGGGCTGTAGAAGAGTTGTTGGGGAAGGAGGGGGGCTGAGGAGGGG GCATCTCCCAACTTCTCCCTTTTGGACCCTGCCGAAGCTCCCTGCCTTTAATAAACTGGCCA AGTGTGGAAAAA ·

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FIGURE 233

MRASLLLSVLRPAGPVAVGISLGFTLSLLSVTWVEEPCGPGPPQPGDSELPPRGNTNAARRP
NSVQPGAEREKPGAGEGAGENWEPRVLPYHPAQPGQAAKKAVRTRYISTELGIRQRLLVAVL
TSQTTLPTLGVAVNRTLGHRLERVVFLTGARGRRAPPGMAVVTLGEERPIGHLHLALRHLLE
QHGDDFDWFFLVPDTTYTEAHGLARLTGHLSLASAAHLYLGRPQDFIGGEPTPGRYCHGGFG
VLLSRMLLQQLRPHLEGCRNDIVSARPDEWLGRCILDATGVGCTGDHEGVHYSHLELSPGEP
VQEGDPHFRSALTAHPVRDPVHMYQLHKAFARAELERTYQEIQELQWEIQNTSHLAVDGDRA
AAWPVGIPAPSRPASRFEVLRWDYFTEQHAFSCADGSPRCPLRGADRADVADVLGTALEELN
RRYHPALRLQKQQLVNGYRRFDPARGMEYTLDLQLEALTPQGGRRPLTRRVQLLRPLSRVEI
LPVPYVTEASRLTVLLPLAAAERDLAPGFLEAFATAALEPGDAAAALTLLLLYEPRQAQRVA
HADVFAPVKAHVAELERRFPGARVPWLSVQTAAPSPLRLMDLLSKKHPLDTLFLLAGPDTVL
TPDFLNRCRMHAISGWQAFFPMHFQAFHPGVAPPQGPGPPELGRDTGRFDRQAASEACFYNS
DYVAARGRLAAASEQEEELLESLDVYELFLHFSSLHVLRAVEPALLQRYRAQTCSARLSEDL
YHRCLQSVLEGLGSRTQLAMLLFEQEQGNST

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FIGURE 234

GCTCTGGCCGGCCGGCGATTGGTCACCGCCGCTAGGGGACAGCCCTGGCCTCCTCTGAT TGGCAAGCGCTGGCCACCTCCCACACCCTTGCGAACGCTCCCCTAGTGGAGAAAAGGAGT AGCTATTAGCCAATTCGGCAGGGCCCGCTTTTTAGAAGCTTGATTTCCTTTGAAGATGAAAG ACTAGCGGAAGCTCTGCCTCTTTCCCCAGTGGGCGAGGGAACTCGGGGCGATTGGCTGGGAA CTGTATCCACCCAAATGTCACCGATTTCTTCCTATGCAGGAAATGAGCAGACCCATCAATAA GAAATTTCTCAGCCTGGCCGAAAATGGTTGGCCCCACGAAGCCACGACAACTGGAGGCAAAG AGGGTTGCTCAACGCCCCGCCTCATTGGAAAACCAAATCAGATCTGGGACCTATATAGCGTG GCGGAGGCGGGCGATGATTGTCGCGCTCGCACCCACTGCAGCTGCGCACAGTCGCATTTCT TTCCCCGCCCTGAGACCCTGCAGCACCATCTGTCATCGCGGCTGGGCTGTTTGGTTTGAGC ATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCTGTGGCGGGAAAGCGGCCCCCAGAAC CGACCACACCGTGGCAAGAGGACCCAGAACCCGAGGACGAAAACTTGTATGAGAAGAACCCA GACTCCCATGGTTATGACAAGGACCCCGTTTTGGACGTCTGGAACATGCGACTTGTCTTCTT CTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACCTTTGTGGCCTATCTGCCTGACTACA GGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCTTGTGAAATACCGAGAGGCCAATGGC CTTCCCATCATGGAATCCAACTGCTTCGACCCCAGCAAGATCCAGCTGCCAGAGGATGAGTG CTCTTCTCAGAGCACCTAATTAAAGGGGCTGAAAGTCTGAA

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FIGURE 235

MAAGLFGLSARRLLAAAATRGLPAARVRWESSFSRTVVAPSAVAGKRPPEPTTPWQEDPEPE DENLYEKNPDSHGYDKDPVLDVWNMRLVFFFGVSIILVLGSTFVAYLPDYRMKEWSRREAER LVKYREANGLPIMESNCFDPSKIQLPEDE

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FIGURE 236

GGCGGCTGGGCTGTTTGGTTTGAGCGCTCGCCGTCTTTTTGGCGGCAGCGGCGACGCGAGGGC
TCCCGGCCGCCCGCGTCCGCTGGGAATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCT
GTGGCGGGAAAGCGGCCCCCAGAACCGACCACACCGTGGCAAGAGGACCCAGAACCCGAGGA
CGAAAACTTGTATGAGAAGAACCCAGACTCCCATGGTTATGACAAGGACCCCGTTTTGGACG
TCTGGAACATGCGACTTGTCTTCTTCTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACC
TTTGTGGCCTATCTGCCTGACTACAGGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCT
TGTGAAATACCGAGAGGCCAATGGCCTTCCCATCATGGAATCCAACTGCTTCGACCCCAGCA
AGATCCAG

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FIGURE 237

GCGGCGGCT**ATG**CCGCTTGCTCTGCTCGTGCTCCTGGGGGCCCGGCGGCTGGTGCCT TGCAGAACCCCCACGCGACAGCCTGCGGGAGGAACTTGTCATCACCCCGCTGCCTTCCGGGG ACGTAGCCGCCACATTCCAGTTCCGCACGCGCTGGGATTCGGAGCTTCAGCGGGAAGGAGTG TCCCATTACAGGCTCTTTCCCAAAGCCCTGGGGCAGCTGATCTCCAAGTATTCTCTACGGGA GCTGCACCTGTCATTCACACAAGGCTTTTGGAGGACCCGATACTGGGGGGCCACCCTTCCTGC AGGCCCCATCAGGTGCAGAGCTGTGGGTCTGGTTCCAAGACACTGTCACTGATGTGGATAAA TCTTGGAAGGAGCTCAGTAATGTCCTCTCAGGGATCTTCTGCGCCTCTCTCAACTTCATCGA CTCCACCAACACACTCCCCACTGCCTCCTTCAAACCCCTGGGTCTGGCCAATGACACTG ACCACTACTTTCTGCGCTATGCTGTGCTGCCGCGGGAGGTGGTCTGCACCGAAAACCTCACC CCCTGGAAGAGCTCTTGCCCTGTAGTTCCAAGGCAGGCCTCTCTGTGCTGCTGAAGGCAGA TCGCTTGTTCCACACCAGCTACCACTCCCAGGCAGTGCATATCCGCCCTGTTTGCAGAAATG CACGCTGTACTAGCATCTCCTGGGAGCTGAGGCAGACCCTGTCAGTTGTATTTGATGCCTTC ATCACGGGGCAGGGAAAGAAGACTGGTCCCTCTTCCGGATGTTCTCCCGAACCCTCACGGA GCCCTGCCCCTGGCTTCAGAGAGCCGAGTCTATGTGGACATCACCACCTACAACCAGGACA ACGAGACATTAGAGGTGCACCCACCCCGACCACTACATATCAGGACGTCATCCTAGGCACT CGGAAGACCTATGCCATCTATGACTTGCTTGACACCGCCATGATCAACAACTCTCGAAACCT CAACATCCAGCTCAAGTGGAAGAGACCCCCAGAGAATGAGGCCCCCCAGTGCCCTTCCTGC ATGCCCAGCGGTACGTGAGTGGCTATGGGCTGCAGAAGGGGGAGCTGAGCACACTGCTGTAC AACACCCACCCATACCGGGCCTTCCCGGTGCTGCTGGACACCGTACCCTGGTATCTGCG GCTGTATGTGCACACCCTCACCATCACCTCCAAGGGCAAGGAGAACAAACCAAGTTACATCC ACTACCAGCCTGCCCAGGACCGGCTGCAACCCCACCTCCTGGAGATGCTGATTCAGCTGCCG GCCAACTCAGTCACCAAGGTTTCCATCCAGTTTGAGCGGGCGCTGCTGAAGTGGACCGAGTA CACGCCAGATCCTAACCATGGCTTCTATGTCAGCCCATCTGTCCTCAGCGCCCTTGTGCCCA GCATGGTAGCAGCCAAGCCAGTGGACTGGGAAGAGAGTCCCCTCTTCAACAGCCTGTTCCCA GTCTCTGATGGCTCTAACTACTTTGTGCGGCTCTACACGGAGCCGCTGCTGGTGAACCTGCC GACACCGGACTTCAGCATGCCCTACAACGTGATCTGCCTCACGTGCACTGTGGTGGCCGTGT GCTACGGCTCCTTCTACAATCTCCTCACCCGAACCTTCCACATCGAGGAGCCCCGCACAGGT GGCCTGGCCAAGCGCTGGCCAACCTTATCCGGCGCGCCCGAGGTGTCCCCCCACTC**TGA**TT CTTGCCCTTTCCAGCAGCTGCAGCTGCCGTTTCTCTCTGGGGAGGGGAGCCCAAGGGCTGTT TCTGCCACTTGCTCTCCTCAGAGTTGGCTTTTGAACCAAAGTGCCCTGGACCAGGTCAGGGC CTACAGCTGTGTTGTCCAGTACAGGAGCCACGAGCCAAATGTGGCATTTGAATTTGAATTAA CTTAGAAATTCATTTCCTCACCTGTAGTGGCCACCTCTATATTGAGGTGCTCAATAAGCAAA AGTGGTCGGTGGCTGTATTGGACAGCACAGAAAAAGATTTCCATCACCACAGAAAGGTC GGCTGGCAGCACTGGCCAAGGTGATGGGGTGTGCTACACAGTGTATGTCACTGTGTAGTGGA

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FIGURE 238

MPLALLVLLLGPGGWCLAEPPRDSLREELVITPLPSGDVAATFQFRTRWDSELQREGVSHY
RLFPKALGQLISKYSLRELHLSFTQGFWRTRYWGPPFLQAPSGAELWVWFQDTVTDVDKSWK
ELSNVLSGIFCASLNFIDSTNTVTPTASFKPLGLANDTDHYFLRYAVLPREVVCTENLTPWK
KLLPCSSKAGLSVLLKADRLFHTSYHSQAVHIRPVCRNARCTSISWELRQTLSVVFDAFITG
QGKKDWSLFRMFSRTLTEPCPLASESRVYVDITTYNQDNETLEVHPPPTTTYQDVILGTRKT
YAIYDLLDTAMINNSRNLNIQLKWKRPPENEAPPVPFLHAQRYVSGYGLQKGELSTLLYNTH
PYRAFPVLLLDTVPWYLRLYVHTLTITSKGKENKPSYIHYQPAQDRLQPHLLEMLIQLPANS
VTKVSIQFERALLKWTEYTPDPNHGFYVSPSVLSALVPSMVAAKPVDWEESPLFNSLFPVSD
GSNYFVRLYTEPLLVNLPTPDFSMPYNVICLTCTVVAVCYGSFYNLLTRTFHIEEPRTGGLA
KRLANLIRRARGVPPL

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FIGURE 239

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FIGURE 240

MGSSSFLVLMVSLVLVTLVAVEGVKEGIEKAGVCPADNVRCFKSDPPQCHTDQDCLGERKCC YLHCGFKCVIPVKELEEGGNKDEDVSRPYPEPGWEAKCPGSSSTRCPQK

Signal sequence:

amino acids 1-19

N-myristoylation sites:

amino acids 23-29, 27-33, 32-38, 102-108

WAP-type 'four-disulfide core' domain signature:

amino acids 49-63

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FIGURE 241

AAACTCAGCACTTGCCGGAGTGGCTCATTGTTAAGACAAAGGGTGTGCACTTCCTGGCCAGG AAACCTGAGCGGTGAGACTCCCAGCTGCCTACATCAAGGCCCCAGGACATGCAGAACCTTCC TCTAGAACCCGACCACCACCATGAGGTCCTGCCTGTGGAGATGCAGGCACCTGAGCCAAGG CGTCCAGTGGTCCTTGCTTCTGGCTGTCTTGTTTTCTCTTCGCCTTGCCCTCTTTTA CTACAGTCCCTGGCAAAGCCTAAGTCCCAGGCACCCACAAGGGCGAGGAGGACAACCATCTA TGCAGAGCCAGCGCCAGAGAACAATGCCCTCAACACACAAACCCAGCCCAAGGCCCACACCA ACAGCACAGAGGGCAGCATGGAAGAGCCCAGAAAAAGAGAAAACCATGGTGAACACACTGTC ACCCAGAGGGCAAGATGCAGGGATGGCCTCTGGCAGGACAGAGGCACAATCATGGAAGAGCC AGGACACAAGACGACCCAAGGAAATGGGGGCCAGACCAGGAAGCTGACGGCCTCCAGGACG GTGTCAGAGAAGCACCAGGGCAAAGCGGCAACCACAGCCAAGACGCTCATTCCCAAAAGTCA GCACAGAATGCTGGCTCCCACAGGAGCAGTGTCAACAAGGACGAGACAGAAAGGAGTGACCA CAGCAGTCATCCCACCTAAGGAGAAGAAACCTCAGGCCACCCCACCCCCTGCCCCTTTCCAG AGCCCCACGACGCAGAGAAACCAAAGACTGAAGGCCGCCAACTTCAAATCTGAGCCTCGGTG GGATTTTGAGGAAAAATACAGCTTCGAAATAGGAGGCCTTCAGACGACTTGCCCTGACTCTG TGAAGATCAAAGCCTCCAAGTCGCTGTGGCTCCAGAAACTCTTTCTGCCCAACCTCACTCTC TTCCTGGACTCCAGACACTTCAACCAGAGTGAGTGGGACCGCCTGGAACACTTTGCACCACC CTTTGGCTTCATGGAGCTCAACTACTCCTTGGTGCAGAAGGTCGTGACACGCTTCCCTCCAG TGCCCCAGCAGCAGCTGCTCCTGGCCAGCCTCCCGCTGGGAGCCTCCGGTGCATCACCTGT GCCGTGGTGGGCAACGGGGGCATCCTGAACAACTCCCACATGGGCCAGGAGATAGACAGTCA CGACTACGTGTTCCGATTGAGCGGAGCTCTCATTAAAGGCTACGAACAGGATGTGGGGACTC GGACATCCTTCTACGGCTTTACCGCCTTCTCCCTGACCCAGTCACTCCTTATATTGGGCAAT CGGGGTTTCAAGAACGTGCCTCTTGGGAAGGACGTCCGCTACTTGCACTTCCTGGAAGGCAC CCGGGACTATGAGTGGCTGGAAGCACTGCTTATGAATCAGACGGTGATGTCAAAAAACCTTT TCTGGTTCAGGCACAGACCCCAGGAAGCTTTTCGGGAAGCCCTGCACATGGACAGGTACCTG TTGCTGCACCCAGACTTTCTCCGATACATGAAGAACAGGTTTCTGAGGTCTAAGACCCTGGA TGGTGCCCACTGGAGGATATACCGCCCCACCACTGGGGCCCTCCTGCTGCTCACTGCCCTTC AGCTCTGTGACCAGGTGAGTGCTTATGGCTTCATCACTGAGGGCCATGAGCGCTTTTCTGAT CACTACTATGATACATCATGGAAGCGGCTGATCTTTTACATAAACCATGACTTCAAGCTGGA GAGAGAAGTCTGGAAGCGGCTACACGATGAAGGGATAATCCGGCTGTACCAGCGTCCTGGTC CCGGAACTGCCAAAGCCAAGAAC**TGA**CCGGGGCCAGGGCTGCCATGGTCTCCTTGCCTGCTC CAAGGCACAGGATACAGTGGGAATCTTGAGACTCTTTGGCCATTTCCCATGGCTCAGACTAA GCTCCAAGCCCTTCAGGAGTTCCAAGGGAACACTTGAACCATGGACAAGACTCTCTCAAGAT GGCAAATGGCTAATTGAGGTTCTGAAGTTCTTCAGTACATTGCTGTAGGTCCTGAGGCCAGG GATTTTTAATTAAATGGGGTGATGGGTGGCCAATACCACAATTCCTGCTGAAAAACACTCTT CCAGTCCAAAAGCTTCTTGATACAGAAAAAAGAGCCTGGATTTACAGAAACATATAGATCTG GTTTGAATTCCAGATCGAGTTTACAGTTGTGAAATCTTGAAGGTATTACTTAACTTCACTAC AGATTGTCTAGAAGACCTTTCTAGGAGTTATCTGATTCTAGAAGGGTCTATACTTGTCCTTG TCTTTAAGCTATTTGACAACTCTACGTGTTGTAGAAAACTGATAATAATACAAATGATTGTT

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FIGURE 242

MRSCLWRCRHLSQGVQWSLLLAVLVFFLFALPSFIKEPQTKPSRHQRTENIKERSLQSLAKP
KSQAPTRARRTTIYAEPAPENNALNTQTQPKAHTTGDRGKEANQAPPEEQDKVPHTAQRAAW
KSPEKEKTMVNTLSPRGQDAGMASGRTEAQSWKSQDTKTTQGNGGQTRKLTASRTVSEKHQG
KAATTAKTLIPKSQHRMLAPTGAVSTRTRQKGVTTAVIPPKEKKPQATPPPAPFQSPTTQRN
QRLKAANFKSEPRWDFEEKYSFEIGGLQTTCPDSVKIKASKSLWLQKLFLPNLTLFLDSRHF
NQSEWDRLEHFAPPFGFMELNYSLVQKVVTRFPPVPQQQLLLASLPAGSLRCITCAVVGNGG
ILNNSHMGQEIDSHDYVFRLSGALIKGYEQDVGTRTSFYGFTAFSLTQSLLILGNRGFKNVP
LGKDVRYLHFLEGTRDYEWLEALLMNQTVMSKNLFWFRHRPQEAFREALHMDRYLLLHPDFL
RYMKNRFLRSKTLDGAHWRIYRPTTGALLLLTALQLCDQVSAYGFITEGHERFSDHYYDTSW
KRLIFYINHDFKLEREVWKRLHDEGIIRLYQRPGPGTAKAKN

Cytoplasmic Domain:

amino acids 1-10

Type II Transmembrane Domain:

amino acids 11-35

Lumenal catalytic Domain:

amino acids 36-600

Ribonucleotide Reductase small subunit Signature:

amino acids 481-496

N-glycosylation Sites:

amino acids 300-303, 311-314, 331-334, 375-378, 460-463

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FIGURE 243

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FIGURE 244

MRGPGHPLLLGLLLVLGPSPEQRVEIVPRDLRMKDKFLKHLTGPLYFSPKCSKHFHRLYHNT RDCTIPAYYKRCARLLTRLAVSPVCMEDK

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FIGURE 245

GGGCTGGGCCCGCCGCAGCTCCAGCTGGCCGGCTTGGTCCTGCGGTCCCTTCTCTGGGAGG CCCGACCCGGCCGCGCCCAGCCCCACATGCCACCGCGGGGCTCCGCCGGGCCGCCGC CTCACCGCAATCGCTCTGTTGGTGCTGGGGGCCTCCCCTGGTGCTGGCCGGCGAGGACTGCCT GTGGTACCTGGACCGGAATGGCTCCTGGCATCCGGGGTTTAACTGCGAGTTCTTCACCTTCT GCTGCGGGACCTGCTACCATCGGTACTGCTGCAGGGACCTGACCTTGCTTATCACCGAGAGG CAGCAGAAGCACTGCCTGGCCTCAGCCCCAAGACCATAGCAGGCATCGCCTCAGCTGTGAT CCTCTTTGTTGCTGTGCTGCCACCACCATCTGCTGCTTCCTGTTCCTGTTGCTACCTGT ACCGCCGGCCCAGCAGCTCCAGAGCCCATTTGAAGGCCAGGAGATTCCAATGACAGGCATC CCAGTGCAGCCAGTATACCCATACCCCCAGGACCCCAAAGCTGGCCCTGCACCCCCACAGCC TGGCTTCATGTACCCACCTAGTGGTCCTGCTCCCCAATATCCACTCTACCCAGCTGGGCCCC CAGTCTACAACCCTGCAGCTCCTCCCTATATGCCACCACAGCCCTCTTACCCGGGAGCC TGAGGAACCAGCCATGTCTCTGCTGCCCCTTCAGTGATGCCAACCTTGGGAGATGCCCTCAT CCTGTACCTGCATCTGGTCCTGGGGGTGGCAGGAGTCCTCCAGCCACCAGGCCCCAGACCAA GCCAAGCCCTGGGCCCTACTGGGGACAGAGCCCCAGGGAAGTGGAACAGGAGCTGAACTAGA ACTATGAGGGGTTGGGGGGGGGCTTGGAATTATGGGCTATTTTTACTGGGGGCAAGGGAGG GAGATGACAGCCTGGGTCACAGTGCCTGTTTTCAAATAGTCCCTCTGCTCCCAAGATCCCAG TCCGTCAGCAGCTGGCAGTAGCCCTCTCTCTGGCTGCCCCACTGGCCACATCTCTGGCCTG CTAGATTAAAGCTGTAAAGACAAAA

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FIGURE 246

MPPAGLRRAAPLTAIALLVLGAPLVLAGEDCLWYLDRNGSWHPGFNCEFFTFCCGTCYHRYC CRDLTLLITERQQKHCLAFSPKTIAGIASAVILFVAVVATTICCFLCSCCYLYRRRQQLQSP FEGQEIPMTGIPVQPVYPYPQDPKAGPAPPQPGFMYPPSGPAPQYPLYPAGPPVYNPAAPPP YMPPQPSYPGA

Transmembrane Domains:

amino acids 10-28, 85-110

N-glycosylation Site:

amino acids 38-41

N-myristoylation Sites:

amino acids 5-10, 88-93

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FIGURE 247

GGGGGAGCTAGGCCGGCGGCAGTGGTGGTGGCGGCGCGCCAAGGGTGAGGGCGGCCCCAGAA CCCCAGGTAGGTAGAGCAAGAAGATGGTGTTTTCTGCCCCTCAAATGGTCCCTTGCAACCATG TCATTTCTACTTTCCTCACTGTTGGCTCTCTTAACTGTGTCCACTCCTTCATGGTGTCAGAG CACTGAAGCATCTCCAAAACGTAGTGATGGGACACCATTTCCTTGGAATAAAATACGACTTC ATTGGTGAAATCTGTGACTGTTGCTGAAGGACTCATAGAAGACCATTTTGATGTCACTGTGA
AGATGAGCACCTATCTGGTGGCCTTCATCATTTCAGATTTTGAGTCTGTCAGCAAGATAACC
AAGAGTGGAGTCAAGGTTTCTGTTTTATGCTGTGCCAGACAAGATAAATCAAGCAGATTATGC
ACTGGATGCTGCGGTGACTCTTCTAGAATTTTATGAGGATTATTTCAGCATACCGTATCCCC
TACCCAAACAAGATCTTGCTGCTATTCCCGACTTTCAGTCTGGTGCTATGGAAAACTGGGGA
CTGACAACATATAGAGAATCTGCTCTGTTGTTTGATGCAGAAAAGTCTTCTGCATCAAGTAA
GCTTGGCATCACAGTGACTGGCCCATGAACTGGCCCACCAGTGGTTTTGGGAACCTGGTCA
CTATGGAATGGTGGACCCATCTTGAACTTGAAGTTTGCCAAAATTTATGGAGTTTTGA
TCTGTCAGTGTGACCCATCCTGAACTTGAACTTGAAAGTTTGCACAATTTATGCACAAATTTGA CGCAATGGAGGTAGATGCTTTAAATTCCTCACACCCTGTGTCTACACCTGTGGAAAATCCTG CGCAATGGAGGTAGATGCTTTAAATTCCTCACACCCTGTGTCTACACCTGTGGAAAATCCTG
CTCAGATCCGGGAGATGTTTGATGATGTTTCTTATGATAAGGGAGCTTGTATTCTGAATATG
CTAAGGGAGTATCTTAGCGCTGACGCATTTAAAAGTGGTATTGTACAGTATCTCCAGAAGCA
TAGCTATAAAAATACAAAAAACGAGGACCTGTGGGATAGTATGGCAAGTATTTGCCCTACAG
ATGGTGTAAAAGGGATGGATGGATGTCTCTAGAAGTCAACATTCATCATCACAT
TGGCATCAGGAAGGGGTGGATGTGAAAACCATGAACACTTGGACACTGCAGAGGGGTTT
TCCCCTAATAACCATCACAGGGGGGAGGAATGTACACATGAAGCAAGAGCACTACATGA
AGGGCTCTGACGGCCCCCGGACACTGGGTACCTGGCATGACATCACCC
AGAAATCCAACATGGTCCATCAAATTTTAATGTGCCCATGAATGCCTATTACCATTACCC CAGGAACCCAGTAGGATACCCACTGGCCTGGCAATTTCTGAGGAAAAACTGGAACAAACTTG TACAAAAGTTTGAACTTGGCTCATCTTCCATAGCCCACATGGTAATGGGTACAACAAATCAA ATAAGAATTTTGATAAAATCAGAGTGTGGCTGCAAAGTGAAAAGCTTGAACGTATG**TAA**AAA TTCCTCCCTTGCCCGGTTCCTGTTATCTCTAATCACCAACATTTTGTTGAGTGTATTTTCAAACTAGAGATGGCTGTTTTTGAGTGTATTTTCAAACTAGAGATGGCTGTTTTTGGAGTGTTTTTTTGACTATCCCTGTGAAAAGAATAGCTGTTAGTTTTTCATGAATGGGCTTTTTCATGAATGGGCTATCCCTGCTGCAACGTGTTTTCATCACCAAGTGTTTGGGTTTCCCTGCAACGTAAACCCAAGTGTTGGGT

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FIGURE 248

MVFLPLKWSLATMSFLLSSLLALLTVSTPSWCQSTEASPKRSDGTPFPWNKIRLPEYVIPVH YDLLIHANLTTLTFWGTTKVEITASQPTSTIILHSHHLQISRATLRKGAGERLSEEPLQVLE HPPQEQIALLAPEPLLVGLPYTVVIHYAGNLSETFHGFYKSTYRTKEGELRILASTQFEPTA ARMAFPCFDEPAFKASFSIKIRREPRHLAISNMPLVKSVTVAEGLIEDHFDVTVKMSTYLVA FIISDFESVSKITKSGVKVSVYAVPDKINOADYALDAAVTLLEFYEDYFSIPYPLPKODLAA IPDFQSGAMENWGLTTYRESALLFDAEKSSASSKLGITVTVAHELAHQWFGNLVTMEWWNDL WLNEGFAKFMEFVSVSVTHPELKVGDYFFGKCFDAMEVDALNSSHPVSTPVENPAQIREMFD DVSYDKGACILNMLREYLSADAFKSGIVOYLOKHSYKNTKNEDLWDSMASICPTDGVKGMDG FCSRSQHSSSSSHWHQEGVDVKTMMNTWTLQRGFPLITITVRGRNVHMKQEHYMKGSDGAPD TGYLWHVPLTFITSKSNMVHRFLLKTKTDVLILPEEVEWIKFNVGMNGYYIVHYEDDGWDSL TGLLKGTHTAVSSNDRASLINNAFQLVSIGKLSIEKALDLSLYLKHETEIMPVFQGLNELIP MYKLMEKRDMNEVETQFKAFLIRLLRDLIDKQTWTDEGSVSEQMLRSELLLLACVHNYQPCV QRAEGYFRKWKESNGNLSLPVDVTLAVFAVGAQSTEGWDFLYSKYQFSLSSTEKSQIEFALC RTQNKEKLQWLLDESFKGDKIKTQEFPQILTLIGRNPVGYPLAWQFLRKNWNKLVQKFELGS SSIAHMVMGTTNQFSTRTRLEEVKGFFSSLKENGSQLRCVQQTIETIEENIGWMDKNFDKIR VWLQSEKLERM

Signal peptide:

amino acids 1-34

N-glycosylation sites:

amino acids 70-74, 154-158, 414-418, 760-764, 901-905

Neutral zinc metallopeptidases, zinc-binding region signature:

amino acids 350-360

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FIGURE 249

CAGCCACAGACGGGTCATGAGCGCGGTATTACTGCTGGCCCTCCTGGGGTTCATCCTCCCAC TGCCAGGAGTGCAGGCGCTGCTCTGCCAGTTTGGGACAGTTCAGCATGTGTGGAAGGTGTCC GACCTACCCCGGCAATGGACCCCTAAGAACACCAGCTGCGACAGCGGCTTGGGGTGCCAGGA CACGTTGATGCTCATTGAGAGCGGACCCCAAGTGAGCCTGGTGCTCTCCAAGGGCTGCACGG AGGCCAAGGACCAGGAGCCCGGGTCACTGAGCACCGGATGGGCCCCGGCCTCTCCCTGATC TTGGGCCCCACAGCCCCAGCAGACCCAGGATCCTTGAGGTGCCCAGTCTGCTTGTCTATGG AAGGCTGTCTGGAGGGGACAACAGAAGAGATCTGCCCCAAGGGGACCACACTGTTATGAT CCAGCCAGGTTGCAACCTGCTCAATGGGACACAGGAAATTGGGCCCGTGGGTATGACTGAGA ACTGCAATAGGAAAGATTTTCTGACCTGTCATCGGGGGACCACCATTATGACACACGGAAAC TTGGCTCAAGAACCCACTGATTGGACCACATCGAATACCGAGATGTGCGAGGTGGGGCAGGT GTGTCAGGAGACGCTGCTCATAGATGTAGGACTCACATCAACCCTGGTGGGGACAAAAG GCTGCAGCACTGTTGGGGCTCAAAATTCCCAGAAGACCACCATCCACTCAGCCCCTCCTGGG GTGCTTGTGGCCTCCTATACCCACTTCTGCTCCTCGGACCTGTGCAATAGTGCCAGCAGCAG CAGCGTTCTGCTGAACTCCCTCCTCCTCAAGCTGCCCCTGTCCCAGGAGACCGGCAGTGTC CTACCTGTGTGCAGCCCCTTGGAACCTGTTCAAGTGGCTCCCCCGAATGACCTGCCCCAGG GGCGCCACTCATTGTTATGATGGGTACATTCATCTCTCAGGAGGTGGGCTGTCCACCAAAAT GAGCATTCAGGGCTGCGTGGCCCAACCTTCCAGCTTCTTGTTGAACCACACCAGACAAATCG GGGGCTGAGGGCCTGGAGTCTCTCACTTGGGGGGTGGGGCTGGCACTGGCCCCAGCGCTGTG GTGGGGAGTGGTTTGCCCTTCCTGCTAACTCTATTACCCCCACGATTCTTCACCGCTGCTGA CCACCCACACTCAACCTCCTCTGACCTCATAACCTAATGGCCTTGGACACCAGATTCTTTC ACACTGGGGAGAGCCTGGAGCATCCGGACTTGCCCTATGGGAGAGGGGACGCTGGAGGAGTG GCTGCATGTATCTGATAATACAGACCCTGTCCTTTCA

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FIGURE 250

MSAVLLLALLGFILPLPGVQALLCQFGTVQHVWKVSDLPRQWTPKNTSCDSGLGCQDTLMLI
ESGPQVSLVLSKGCTEAKDQEPRVTEHRMGPGLSLISYTFVCRQEDFCNNLVNSLPLWAPQP
PADPGSLRCPVCLSMEGCLEGTTEEICPKGTTHCYDGLLRLRGGGIFSNLRVQGCMPQPGCN
LLNGTQEIGPVGMTENCNRKDFLTCHRGTTIMTHGNLAQEPTDWTTSNTEMCEVGQVCQETL
LLIDVGLTSTLVGTKGCSTVGAQNSQKTTIHSAPPGVLVASYTHFCSSDLCNSASSSSVLLN
SLPPQAAPVPGDRQCPTCVQPLGTCSSGSPRMTCPRGATHCYDGYIHLSGGGLSTKMSIQGC
VAQPSSFLLNHTRQIGIFSAREKRDVQPPASQHEGGGAEGLESLTWGVGLALAPALWWGVVC
PSC

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FIGURE 251

CAGGATGAGGGGGAATCTGGCCCTGGTGGGCGTTCTAATCAGCCTGGCCTTCCTGTCACTGCTG CCATCTGGACATCCTCAGCCGGCTGGCGATGACGCCTGCTCTGTGCAGATCCTCGTCCCTGG CCTCAAAGGGGATGCGGGAGAGAGGGAGACAAAGGCGCCCCCGGACGGCCTGGAAGAGTCG GCCCCACGGGAGAAAAGGAGACATGGGGGACAAAGGACAGAAAGGCAGTGTGGGTCGTCAT GGAAAAATTGGTCCCATTGGCTCTAAAGGTGAGAAAGGAGATTCCGGTGACATAGGACCCCC AGATGGACAACCAGGTCTCTCAGCTGACCAGCGAGCTCAAGTTCATCAAGAATGCTGTCGCC GGTGTGCGCGAGACGGAGACCAAGATCTACCTGCTGGTGAAGGAGGAGAAGCGCTACGCGGA CGCCCAGCTGTCCTGCCAGGGCCGCGGGGCACGCTGAGCATGCCCAAGGACGAGGCTGCCA ATGGCCTGATGGCCGCATACCTGGCGCAAGCCGGCCTGGCCCGTGTCTTCATCGGCATCAAC GACCTGGAGAAGGAGGCCCTTCGTGTACTCTGACCACTCCCCCATGCGGACCTTCAACAA GTGGCGCAGCGTGAGCCCAACAATGCCTACGACGAGGAGGACTGCGTGGAGATGGTGGCCT CGGGCGGCTGGAACGACGTGGCCTGCCACACCACCATGTACTTCATGTGTGAGTTTGACAAG GAGAACATG<u>TGA</u>GCCTCAGGCTGGGGCTGCCCATTGGGGGCCCCACATGTCCCTGCAGGGTT GGCAGGGACAGACCCAGGTGCCAGCCAGGGAGCTGTCCCTCTGTGAAGGGTGGAG GCTCACTGAGTAGAGGGCTGTTGTCTAAACTGAGAAAATGGCCTATGCTTAAGAGGAAAATG AAAGTGTTCCTGGGGTGCTGTCTCTGAAGAAGCAGAGTTTCATTACCTGTATTGTAGCCCCA ATGTCATTATGTAATTATTACCCAGAATTGCTCTTCCATAAAGCTTGTGCCTTTGTCCAAGC

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FIGURE 252

MRGNLALVGVLISLAFLSLLPSGHPQPAGDDACSVQILVPGLKGDAGEKGDKGAPGRPGRVG PTGEKGDMGDKGQKGSVGRHGKIGPIGSKGEKGDSGDIGPPGPNGEPGLPCECSQLRKAIGE MDNQVSQLTSELKFIKNAVAGVRETESKIYLLVKEEKRYADAQLSCQGRGGTLSMPKDEAAN GLMAAYLAQAGLARVFIGINDLEKEGAFVYSDHSPMRTFNKWRSGEPNNAYDEEDCVEMVAS GGWNDVACHTTMYFMCEFDKENM

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FIGURE 253

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTGCAGGAGCACCGGCAG CACCAGTGTGTGAGGGGAGCAGCGGTCCTAGCCAGTTCCTTGATCCTGCCAGACCACC CAGCCCCGGCACAGAGCTGCTCCACAGGCACCATGAGGATCATGCTGCTATTCACAGCCAT TTCCTGGCGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCAGAGACTCTTC AAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAGCACAGATCCTAA GGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGGACTTATGGGCAAGA GGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGTGAGGGTTCCTCGGCCC CTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGGAACAGAGGAGCAGAGACC TTTA<u>TAAGACTCTCCTACGGATGTGAATCAAGAGAACGTCCCCAGCTTTGGCATCCTCAAGT</u> ATCCCCGAGAGCAGAATAGGTACTCCACTTCCGGACTCCTGGACTGCATTAGGAAGACCTC TTTCCCTGTCCCAATCCCCAGGTGCGCACGCTCCTGTTACCCTTTCTCTTCCCTGTTCTTGT AACATTCTTGTGCTTTGACTCCTTCTCCATCTTTTCTACCTGACCCTGGTGTGGAAACTGCA TAGTGAATATCCCCAACCCCAATGGGCATTGACTGTAGAATACCCTAGAGTTCCTGTAGTGT CCTACATTAAAAATATAATGTCTCTCTATTCCTCAACAATAAAGGATTTTTGCATATGAA

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FIGURE 254

MRIMLLFTAILAFSLAQSFGAVCKEPQEEVVPGGGRSKRDPDLYQLLQRLFKSHSSLEGLLK ALSQASTDPKESTSPEKRDMHDFFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLGSTGK SSLGTEEQRPL

Important features:

Signal peptide:

amino acids 1-18

Tyrosine kinase phosphorylation site.

amino acids 36-45

N-myristoylation site.

amino acids 33-39, 59-65

Amidation site.

amino acids 90-94

Leucine zipper pattern.

amino acids 43-65

Tachykinin family signature.

amino acids 86-92

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FIGURE 255

GGGCGTCTCCGGCTGCTCCTATTGAGCTGTCTCGCTGTGCCCGCTGTGCCTGCTGTGCC CGCGCTGTCGCCGCTGCTACCGCGTCTGCTGGACGCGGGAGACGCCAGCGAGCTGGTGATTG GAGCCCTGCGGAGAGCTCAAGCGCCCAGCTCTGCCCCAGGAGCCCAGGCTGCCCCGTGAGTC CCATAGTTGCTGCAGGAGTGGAGCCATGAGCTGCGTCCTGGGTGTCATCCCCTTGGGGC TGCTGTTCCTGGTCTGCGGATCCCAAGGCTACCTCCTGCCCAACGTCACTCTCTTAGAGGAG CTGCTCAGCAAATACCAGCACAACGAGTCTCACTCCCGGGTCCGCAGAGCCATCCCCAGGGA GGACAAGGAGGAGATCCTCATGCTGCACAACAAGCTTCGGGGCCAGGTGCAGCCTCAGGCCT CCAACATGGAGTACATGGTGAGCGCCGGCTCCGGCCGCAGAGGCTGGCACCGGGGGTGGGGC TTGAGACAGGGTCTCACTCTGCCACTGACGCTGGAGTGCAATGGCACAATCGTCATGCCCTG AAACCT**TAG**ACTCCCGGGGTTAAGCGATCCTGCTTCAGCCTCCCAAGTAGCTGGAACTACAG GCATGCACCATGGTGCCCAGCTAGATTTTAAATATTTTGTGGAGATGGGGGTCTTGCTACGT TGCCCAGGCTGGTCTTGAACTCCTAGGCTCAAGCAATCCTCCTGCCTCAGCCTCTCAAAGTG CTAGGATTATAGGCATGAGTCACCCTGTCTGGCTCTGGCTCTGTTCTTAACATTCTGCCAAA ACAACACGTGGGTTCCCTGTGCAGAGCCTGCCTCGTTGCCTTCATGTCACTCTTGGTAGC TCCACTGGGAACACAGCTCTCAGCCTTTCCCACCTGGAGGCAGAGTGGGGAGGGGCCCAGGG CTGGGCTTTGCTGATGCTGATCTCAGCTGTGCCACACGCTAGCTGCACCACCCTGACTTCTC GTGAGATAAGTCGAGGCTGTGAAGGGCCCGGCACAGACTGACCTGCCTCCCCAACCCCTAGG CTTTGCTAACCGGGAAAGGACTAACGGTGACAGAAGACAGCCAAGGTCAACCCTCCCGGGT GATTGTGATGGGTGTTCCAGGTGTGGTTGGGCGATGCTGCTACTTGACCCCAAGCTCCAGTG TGGAAACTTCCTTCCTGGCTGGTTTTCCAGAACTACAGAGGAATGGACCACAGTCTTCCAGG GTCCCTCGTCCACCAACCGGGAGCCTCCACCTTGGCCATCCGTCAGCTATGAATGGCTT TTTAAACAAACCCACGTCCCAGCCTGGGTAACATGGTAAAGCCCCGTCTCTACAAAAAAATC CAAGTTAGCCGGGCATGGTGGTGCGCACCTGTAGTCCCAGCTGCAGTGGGACTGAGGTGGAG GTGGAGGTGGGGGGTGGGAGCTGAGGAAGGAGGATCGCTTGAGCCTGGGAAGTCGAGGCTGC AGTGAGCTGAGATTGCACCACTGCACTCCAGCCTGGGTGACAGAGCAAGACCCTGTCTCAAAAA

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FIGURE 256

MSCVLGGVIPLGLLFLVCGSQGYLLPNVTLLEELLSKYQHNESHSRVRRAIPREDKEEILML HNKLRGQVQPQASNMEYMVSAGSGRRGWHRGWGLGHQPALFPSQLCSPASACDGWLRVSSGR GGSRLCSVLFVCFETGSHSATDAGVQWHNRHALKP

Important features:

Signal peptide:

amino acids 1-22

N-glycosylation site.

amino acids 27-31, 41-45

N-myristoylation site.

amino acids 126-132, 140-146

Amidation site.

amino acids 85-89

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FIGURE 257

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FIGURE 258

MGSGLPLVLLLTLLGSSHGTGPGMTLQLKLKESFLTNSSYESSFLELLEKLCLLLHLPSGTS VTLHHARSQHHVVCNT

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FIGURE 259

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FIGURE 260

MIGYYLILFLMWGSSTVFCVLLIFTIAEASFSVENECLVDLCLLRICYKLSGVPNQCRVPLP SDCSK

Important features:

Signal peptide:

amino acids 1-29

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FIGURE 261

GAGGATTTGCCACAGCAGCGGATAGAGCAGGAGAGCCACCGGAGCCCTTGAGACATCCTT GAGAAGAGCCACAGCATAAGAGACTGCCCTGCTTGGTGTTTTTGCAGGATGATGGTGGCCCTT CGAGGAGCTTCTGCATTGCTGGTTCTGTTCCTTGCAGCTTTTCTGCCCCCGCCGCAGTGTAC CCAGGACCCAGCCATGGTGCATTACATCTACCAGCGCTTTCGAGTCTTGGAGCAAGGGCTGG AAAAATGTACCCAAGCAACGAGGGCATACATTCAAGAATTCCAAGAGTTCTCAAAAAATATA TCTGTCATGCTGGGAAGATGTCAGACCTACACAAGTGAGTACAAGAGTGCAGTGGGTAACTT ACGAGTGCATCGTATCAGAGGACAAGACACTGGCAGAAATGTTGCTCCAAGAAGCTGAAGAA GAGAAAAAGATCCGGACTCTGCTGAATGCAAGCTGTGACAACATGCTGATGGGCATAAAGTC TTTGAAAATAGTGAAGAAGATGATGGACACACATGGCTCTTGGATGAAAGATGCTGTCTATA ACTCTCCAAAGGTGTACTTATTAATTGGATCCAGAAACAACACTGTTTGGGAATTTGCAAAC ATACGGGCATTCATGGAGGATAACACCAAGCCAGCTCCCCGGAAGCAAATCCTAACACTTTC CTGGCAGGGAACAGGCCAAGTGATCTACAAAGGTTTTCTATTTTTTCATAACCAAGCAACTT CTAATGAGATAATCAAATATAACCTGCAGAAGAGGACTGTGGAAGATCGAATGCTGCTCCCA GGAGGGGTAGGCCGAGCATTGGTTTACCAGCACTCCCCCTCAACTTACATTGACCTGGCTGT GGATGAGCATGGGCCCATCCACTCTGGGCCAGGCACCCATAGCCATTTGGTTCTCA CAAAGATTGAGCCGGGCACACTGGGAGTGGAGCATTCATGGGATACCCCATGCAGAAGCCAG GATGCTGAAGCCTCATTCCTCTTGTGTGGGGGTTCTCTATGTGGTCTACAGTACTGGGGGCCA GGGCCCTCATCGCATCACCTGCATCTATGATCCACTGGGCACTATCAGTGAGGAGGACTTGC CCAACTTGTTCTTCCCCAAGAGACCAAGAAGTCACTCCATGATCCATTACAACCCCAGAGAT AAGCAGCTCTATGCCTGGAATGAAGGAAACCAGATCATTTACAAACTCCAGACAAAGAGAAA GCTGCCTCTGAAG<u>TAA</u>TGCATTACAGCTGTGAGAAAGAGCACTGTGGCTTTGGCAGCTGTTC AGTGTGTAGAAGTGGAAATACGTATGCCTCCTTTCCCAAATGTCACTGCCTTAGGTATCTTC CAAGAGCTTAGATGAGAGCATATCATCAGGAAAGTTTCAACAATGTCCATTACTCCCCCAAA CCTCCTGGCTCTCAAGGATGACCACATTCTGATACAGCCTACTTCAAGCCTTTTGTTTTACT CCCTAATATTCACCACTGGCTTTTCTCTCCCCTGGCCTTTGCTGAAGCTCTTCCCTCTTTTT CAAATGTCTATTGATATTCTCCCATTTTCACTGCCCAACTAAAATACTATTAATATTTCTTT CTTTTCTTTTCTTTTTTGAGACAAGGTCTCACTATGTTGCCCAGGCTGGTCTCAAACTCC AGAGCTCAAGAGATCCTCCTGCCTCAGCCTCCTAAGTACCTGGGATTACAGGCATGTGCCAC CACACCTGGCTTAAAATACTATTTCTTATTGAGGTTTAACCTCTATTTCCCCTAGCCCTGTC CTTCCACTAAGCTTGGTAGATGTAATAATAAAGTGAAAATATTAACATTTGAATATCGCTTT CCAGGTGTGGAGTGTTTGCACATCATTGAATTCTCGTTTCACCTTTGTGAAACATGCACAAG TCTTTACAGCTGTCATTCTAGAGTTTAGGTGAGTAACACAATTACAAAGTGAAAGATACAGC TAGAAAATACTACAAATCCCATAGTTTTTCCATTGCCCAAGGAAGCATCAAATACGTATGTT TGTTCACCTACTCTTATAGTCAATGCGTTCATCGTTTCAGCCTAAAAATAATAGTCTGTCCC TTTAGCCAGTTTTCATGTCTGCACAAGACCTTTCAATAGGCCTTTCAAATGATAATTCCTCC AGAAAACCAGTCTAAGGGTGAGGACCCCAACTCTAGCCTCCTCTTGTCTTGCTGTCCTCTGT

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FIGURE 262

MMVALRGASALLVLFLAAFLPPPQCTQDPAMVHYIYQRFRVLEQGLEKCTQATRAYIQEFQE FSKNISVMLGRCQTYTSEYKSAVGNLALRVERAQREIDYIQYLREADECIVSEDKTLAEMLL QEAEEEKKIRTLLNASCDNMLMGIKSLKIVKKMMDTHGSWMKDAVYNSPKVYLLIGSRNNTV WEFANIRAFMEDNTKPAPRKQILTLSWQGTGQVIYKGFLFFHNQATSNEIIKYNLQKRTVED RMLLPGGVGRALVYQHSPSTYIDLAVDEHGLWAIHSGPGTHSHLVLTKIEPGTLGVEHSWDT PCRSQDAEASFLLCGVLYVVYSTGGQGPHRITCIYDPLGTISEEDLPNLFFPKRPRSHSMIH YNPRDKQLYAWNEGNQIIYKLQTKRKLPLK

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FIGURE 263

GGGCGCCCGCGTACTCACTAGCTGAGGTGGCAGTGGTTCCACCAACATCGGAGCTCTCGCAGA TGTCGGAGCTCATGGGGCTGTCGGTGTTGCTTGGGCTGGCCCTGATGGCGACGGCGGCG **AAATGGATTTCCACCTGACAAATCTTCGGGATCCAAGAAGCAGAAACAATATCAGCGGATTC** GGAAGGAGAACCTCAACAACACACTTCACCCACCGCCTCCTGGCTGCAGCTCTGAAGAGC CACAGCGGGAACATATCTTGCATGGACTTTAGCAGCAATGGCAAATACCTGGCTACCTGTGC AGATGATCGCACCATCCGCATCTGGAGCACCAAGGACTTCCTGCAGCGAGAGCACCGCAGCA TGAGAGCCAACGTGGAGCTGGACCACGCCACCCTGGTGCGCTTCAGCCCTGACTGCAGAGCC TTCATCGTCTGGCTGGCCAACGGGGACACCCTCCGTGTCTTCAAGATGACCAAGCGGGAGGA TGGGGGCTACACCTTCACAGCCACCCCAGAGGACTTCCCTAAAAAGCACAAGGCGCCTGTCA TCGACATTGGCATTGCTAACACAGGGAAGTTTATCATGACTGCCTCCAGTGACACCACTGTC ACACGCTGCTGTATCTCCCTGTGGCAGATTTGTAGCCTCGTGTGGCTTCACCCCAGATGTGA AGGTTTGGGAAGTCTGCTTTGGAAAGAGGGGGGGTTCCAGGAGGTGGTGCGAGCCTTCGAA CTAAAGGGCCACTCGCGGGTTGCACTCGTTTGCTTTCTCCAACGACTCACGGAGGATGGC TTCTGTCTCCAAGGATGGTACATGGAAACTGTGGGACACAGATGTGGAATACAAGAAGAAGC AGGACCCTACTTGCTGAAGACAGGCCGCTTTGAAGAGGCGGCGGTGCCGCGCCGTGCCGC CTGGCCCTCTCCCCCAACGCCCAGGTCTTGGCCTTGGCCAGTGGCAGTAGTATTCATCTCTA CAATACCCGGCGGGCGAGAAGGAGGAGTGCTTTGAGCGGGTCCATGGCGAGTGTATCGCCA ACTTGTCCTTTGACATCACTGGCCGCTTTCTGGCCTCCTGTGGGGACCGGGCGGTGCGGCTG TTTCACAACACTCCTGGCCACCGAGCCATGGTGGAGGAGATGCAGGGCCACCTGAAGCGGGC CTCCAACGAGAGCACCCGCCAGAGGCTGCAGCAGCCTGACCCAGGCCCAAGAGACCCTGA AGAGCCTGGGTGCCCTGAAGAAG**TGA**CTCTGGGAGGGCCCGGCGCAGAGGATTGAGGAGGAG GGATCTGGCCTCATGGCACTGCTGCCATCTTTCCTCCCAGGTGGAAGCCTTTCAGAAGG AGTCTCCTGGTTTTCTTACTGGTGGCCCTGCTTCTTCCCATTGAAACTACTCTTGTCTACTT AGGTCTCTCTTCTTGCTGGCTGTGACTCCTCCCTGACTAGTGGCCAAGGTGCTTTTCTTC CTCCCAGGCCCAGTGGGTGGAATCTGTCCCCACCTGGCACTGAGGAGAATGGTAGAGAGGAG AGGAGAGAGAGAGAATGTGATTTTTGGCCTTGTGGCAGCACATCCTCACACCCAAAGAAG TTTGTAAATGTTCCAGAACAACCTAGAGAACACCTGAGTACTAAGCAGCAGTTTTGCAAGGA TGGGAGACTGGGATAGCTTCCCATCACAGAACTGTGTTCCATCAAAAAGACACTAAGGGATT TCCTTCTGGGCCTCAGTTCTATTTGTAAGATGGAGAATAATCCTCTCTGTGAACTCCTTGCA AAGATGATATGAGGCTAAGAGAATATCAAGTCCCCAGGTCTGGAAGAAAAGTAGAAAAGAGT AGTACTATTGTCCAATGTCATGAAAGTGGTAAAAGTGGGAACCAGTGTGCTTTGAAACCAAA TTAGAAACACATTCCTTGGGAAGGCAAAGTTTTCTGGGACTTGATCATACATTTTATATGGT TGGGACTTCTCTCTCGGGAGATGATATCTTGTTTAAGGAGACCTCTTTTCAGTTCATCAAG

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FIGURE 264

MELSQMSELMGLSVLLGLLALMATAAVARGWLRAGEERSGRPACQKANGFPPDKSSGSKKQK
QYQRIRKEKPQQHNFTHRLLAAALKSHSGNISCMDFSSNGKYLATCADDRTIRIWSTKDFLQ
REHRSMRANVELDHATLVRFSPDCRAFIVWLANGDTLRVFKMTKREDGGYTFTATPEDFPKK
HKAPVIDIGIANTGKFIMTASSDTTVLIWSLKGQVLSTINTNQMNNTHAAVSPCGRFVASCG
FTPDVKVWEVCFGKKGEFQEVVRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWKLWDTDV
EYKKKQDPYLLKTGRFEEAAGAAPCRLALSPNAQVLALASGSSIHLYNTRRGEKEECFERVH
GECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAMVEEMQGHLKRASNESTRQRLQQQLTQ
AQETLKSLGALKK

Important features:

Signal peptide:

amino acids 1-25

N-glycosylation site.

amino acids 76-80, 92-96, 231-235, 289-293, 378-382, 421-425

Beta-transducin family Trp-Asp repeat protein.

amino acids 30-47, 105-118, 107-119, 203-216, 205-217, 296-308

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FIGURE 265

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCAGG CAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTGCCACGCGAGTCTCAATCATGCTCC TCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTCCAGTGT GGGGCAGCCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGCACCCCGCT GGGGCGGAAGGCGAGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTCAGGAAACGCA AGCACCACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCGGACGGCAGGTAC ${\tt CGCTGCTCCATGGACTTGAAGAACATCAATTTT} \underline{{\tt TAG}} {\tt GCGCTTGCCTGGTCTCAGGATACCCA}$ CCATCCTTTTCCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAAACCCAGCTCCCATGAC TCTCCCAGTCCCTACACTGACTACCCTGATCTCTTGTCTAGTACGCACATATGCACACAG GCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCTGAGGATGTCACAGCTTGAGG CTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTCCCTGCTCAGGCTGCCAGAGAGGTGGTA AATGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTGACCTGCTCTCTTTCCTGGGCCCTG CCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAGACATTCCTGGGCACAGGCTCTTGGGT GCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCCTCAGGCCCTTCACGTGAGGTCTGTGAGG ACCAATTTGTGGGTAGTTCATCTTCCCTCGATTGGTTAACTCCTTAGTTTCAGACCACAGAC TCAAGATTGGCTCTTCCCAGAGGGCAGCAGACAGTCACCCCAAGGCAGGTGTAGGGAGCCCA GGGAGGCCAATCAGCCCCTGAAGACTCTGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGA CCTGTGACCTTCTGCCAGAATTGTCATGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGT TAACCACTGAAGCCCCCAATTCCCACAGCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAA TCTAATCTGATATTGACATATTAGAAGGCAATTAGGGTGTTTCCTTAAACAACTCCTTTCCA AGGATCAGCCCTGAGAGCAGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGG TGGGAGCAAGGGACAGGGCAGGGCAGGGCTGAAAGGGCACTGATTCAGACCAGGGAGG CAACTACACCAACATGCTGGCTTTAGAATAAAAGCACCAACTGAAAAAA

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FIGURE 266

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHP GSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

Signal peptide:

amino acids 1-19

Tyrosine kinase phosphorylation site:

amino acids 88-95

N-myristoylation sites:

amino acids 33-39, 35-41, 46-52

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FIGURE 267

AGCGCCCGGGCGTCGGGGCGGTAAAAGGCCGGCAGAAGGGAGGCACTTGAGAA**ATG**TCTTTC CTCCAGGACCCAAGTTTCTTCACCATGGGGATGTGGTCCATTGGTGCAGGAGCCCTGGGGGC TGCTGCCTTGGCATTGCTGCTTGCCAACACAGACGTGTTTCTGTCCAAGCCCCAGAAAGCGG CCCTGGAGTACCTGGAGGATATAGACCTGAAAACACTGGAGAAGGAACCAAGGACTTTCAAA GCAAAGGAGCTATGGGAAAAAAATGGAGCTGTGATTATGGCCGTGCGGAGGCCAGGCTGTTT CCTCTGTCGAGAGGAAGCTGCGGATCTGTCCTCCCTGAAAAGCATGTTGGACCAGCTGGGCG TCCCCCTCTATGCAGTGGTAAAGGAGCACATCAGGACTGAAGTGAAGGATTTCCAGCCTTAT TTCAAAGGAGAATCTTCCTGGATGAAAAGAAAAGTTCTATGGTCCACAAAGGCGGAAGAT GATGTTTATGGGATTTATCCGTCTGGGAGTGTGGTACAACTTCTTCCGAGCCTGGAACGGAG GCTTCTCTGGAAACCTGGAAGGAAGGCTTCATCCTTGGGGGAGTTTTCGTGGTGGGATCA GGAAAGCAGGGCATTCTTCTTGAGCACCGAGAAAAAGAATTTGGAGACAAAGTAAACCTACT TTCTGTTCTGGAAGCTGCTAAGATGATCAAACCACAGACTTTGGCCTCAGAGAAAAAATGAT TGTGTGAAACTGCCCAGCTCAGGGATAACCAGGGACATTCACCTGTGTTCATGGGATGTATT GTTTCCACTCGTGTCCCTAAGGAGTGAGAAACCCATTTATACTCTACTCTCAGTATGGATTA TTAATGTATTTTAATATTCTGTTTAGGCCCACTAAGGCAAAATAGCCCCAAAACAAGACTGA CAAAAATCTGAAAAACTAATGAGGATTATTAAGCTAAAACCTGGGAAATAGGAGGCTTAAAA TTGACTGCCAGGCTGGGTGCAGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCAAGG TGAGCAAGTCACTTGAGGTCGGGAGTTCGAGACCAGCCTGAGCAACATGGCGAAACCCCGTC GGAGGCTGAGGCAGGAGATCACTTGAACCTGGGAGGTGGAGGTTGCGGTGAGCTGAGATCA

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FIGURE 268

MSFLQDPSFFTMGMWSIGAGALGAAALALLLANTDVFLSKPQKAALEYLEDIDLKTLEKEPR TFKAKELWEKNGAVIMAVRRPGCFLCREEAADLSSLKSMLDQLGVPLYAVVKEHIRTEVKDF QPYFKGEIFLDEKKKFYGPQRRKMMFMGFIRLGVWYNFFRAWNGGFSGNLEGEGFILGGVFV VGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK

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FIGURE 269

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FIGURE 270

MANPGLGLLLALGLPFLLARWGRAWGQIQTTSANENSTVLPSSTSSSSDGNLRPEAITAIIV VFSLLAALLLAVGLALLVRKLREKRQTEGTYRPSSEEQFSHAAEARAPQDSKETVQGCLPI

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FIGURE 271

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FIGURE 272

MTFFLSLLLLLVCEAIWRSNSGSNTLENGYFLSRNKENHSQPTQSSLEDSVTPTKAVKTTGK GIVKGRNLDSRGLILGAEAWGRGVKKNT

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FIGURE 273

TTGTCATTGTTATAGATCCTAGTGTGCCAGAAGATGAAAAAATAATTGAACAAATAGAGGAT ATGGTGACTACAGCTTCTACGTACCTGTTTGAAGCCACAGAAAAAAGATTTTTTTCAAAAA TGTATCTATATTAATTCCTGAGAATTGGAAGGAAAATCCTCAGTACAAAAGGCCAAAACATG AAAACCATAAACATGCTGATGTTATAGTTGCACCACCTACACTCCCAGGTAGAGATGAACCA TACACCAAGCAGTTCACAGAATGTGGAGAGAAAGGCGAATACATTCACTTCACCCCTGACCT TCTACTTGGAAAAAAACAAAATGAATATGGACCACCAGGCAAACTGTTTGTCCATGAGTGGG CTCACCTCCGGTGGGGAGTGTTTGATGAGTACAATGAAGATCAGCCTTTCTACCGTGCTAAG TCAAAAAAAATCGAAGCAACAAGGTGTTCCGCAGGTATCTCTGGTAGAAATAGAGTTTATAA GTGTCAAGGAGCAGCTGTCTTAGTAGAGCATCCAGAATTGATTCTTACAACAAAACTGTATG GAAAAGATTGTCAATTCTTTCCTGATAAAGTACAAACAGAAAAAGCATCCATAATGTTTATG CAAAGTATTGATTCTGTTGTTGAATTTTGTAACGAAAAAACCCATAATCAAGAAGCTCCAAG CCTACAAAACATAAAGTGCAATTTTAGAAGTACATGGGAGGTGATTAGCAATTCTGAGGATT TTAAAAACACCATACCCATGGTGACACCACCTCCTCCACCTGTCTTCTCATTGCTGAAGATC AGTCAAAGAATTGTGTGCTTAGTTCTTGATAAGTCTGGAAGCATGGGGGGGTAAGGACCGCCT AAATCGAATGAATCAAGCAGCAAAACATTTCCTGCTGCAGACTGTTGAAAAATGGATCCTGGG TGGGGATGTTCACTTTGATAGTACTGCCACTATTGTAAATAAGCTAATCCAAATAAAAAGC AGTGATGAAAGAAACACTCATGGCAGGATTACCTACATATCCTCTGGGAGGAACTTCCAT CTGCTCTGGAATTAAATATGCATTTCAGGTGATTGGAGAGCTACATTCCCAACTCGATGGAT CCGAAGTACTGCTGCTGACTGATGGGGAGGATAACACTGCAAGTTCTTGTATTGATGAAGTG AAACAAAGTGGGGCCATTGTTCATTTTATTGCTTTGGGAAGAGCTGCTGATGAAGCAGTAAT AGAGATGAGCAAGATAACAGGAGGAAGTCATTTTATGTTTCAGATGAAGCTCAGAACAATG GCCTCATTGATGCTTTTGGGGCTCTTACATCAGGAAATACTGATCTCTCCCAGAAGTCCCTT CAGCTCGAAAGTAAGGGATTAACACTGAATAGTAATGCCTGGATGAACGACACTGTCATAAT TGATAGTACAGTGGGAAAGGACACGTTCTTTCTCATCACATGGAACAGTCTGCCTCCCAGTA TTTCTCTCTGGGATCCCAGTGGAACAATAATGGAAAATTTCACAGTGGATGCAACTTCCAAA ATGGCCTATCTCAGTATTCCAGGAACTGCAAAGGTGGGCACTTGGGCATACAATCTTCAAGC CAAAGCGAACCCAGAAACATTAACTATTACAGTAACTTCTCGAGCAGCAAATTCTTCTGTGC CTCCAATCACAGTGAATGCTAAAATGAATAAGGACGTAAACAGTTTCCCCAGCCCAATGATT GTTTACGCAGAAATTCTACAAGGATATGTACCTGTTCTTGGAGCCAATGTGACTGCTTTCAT TGAATCACAGAATGGACATACAGAAGTTTTGGAACTTTTGGATAATGGTGCAGGCGCTGATT CTTTCAAGAATGATGGAGTCTACTCCAGGTATTTTACAGCATATACAGAAAATGGCAGATAT AGCTTAAAAGTTCGGGCTCATGGAGGAGCAAACACTGCCAGGCTAAAATTACGGCCTCCACT GAATAGAGCCGCGTACATACCAGGCTGGGTAGTGAACGGGGAAATTGAAGCAAACCCGCCAA GACCTGAAATTGATGAGGATACTCAGACCACCTTGGAGGATTTCAGCCGAACAGCATCCGGA GGTGCATTTGTGGTATCACAAGTCCCAAGCCTTCCCTTGCCTGACCAATACCCACCAAGTCA AATCACAGACCTTGATGCCACAGTTCATGAGGATAAGATTATTCTTACATGGACAGCACCAG GAGATAATTTTGATGTTGGAAAAGTTCAACGTTATATCATAAGAATAAGTGCAAGTATTCTT GATCTAAGAGACAGTTTTGATGATGCTCTTCAAGTAAATACTACTGATCTGTCACCAAAGGA GGCCAACTCCAAGGAAAGCTTTGCATTTAAACCAGAAAATATCTCAGAAGAAAATGCAACCC ACATATTTATTGCCATTAAAAGTATAGATAAAAGCAATTTGACATCAAAAGTATCCAACATT GCACAAGTAACTTTGTTTATCCCTCAAGCAAATCCTGATGACATTGATCCTACACCTACTCC TACTCCTACTCCTGATAAAAGTCATAATTCTGGAGTTAATATTTCTACGCTGGTAT TGTCTGTGATTGGGTCTGTTGTAATTGTTAACTTTATTTTAAGTACCACCATT<u>TGA</u>ACCTTA ACGAAGAAAAAATCTTCAAGTAGACCTAGAAGAGAGTTTTAAAAAAACAAAACAATGTAAGT AAAGGATATTTCTGAATCTTAAAATTCATCCCATGTGTGATCATAAAACTCATAAAAATAATT

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FIGURE 274

MGLFRGFVFLLVLCLLHQSNTSFIKLNNNGFEDIVIVIDPSVPEDEKIIEQIEDMVTTASTY
LFEATEKRFFFKNVSILIPENWKENPQYKRPKHENHKHADVIVAPPTLPGRDEPYTKQFTEC
GEKGEYIHFTPDLLLGKKQNEYGPPGKLFVHEWAHLRWGVFDEYNEDQPFYRAKSKKIEATR
CSAGISGRNRVYKCQGGSCLSRACRIDSTTKLYGKDCQFFPDKVQTEKASIMFMQSIDSVVE
FCNEKTHNQEAPSLQNIKCNFRSTWEVISNSEDFKNTIPMVTPPPPPVFSLLKISQRIVCLV
LDKSGSMGGKDRLNRMNQAAKHFLLQTVENGSWVGMVHFDSTATIVNKLIQIKSSDERNTLM
AGLPTYPLGGTSICSGIKYAFQVIGELHSQLDGSEVLLLTDGEDNTASSCIDEVKQSGAIVH
FIALGRAADEAVIEMSKITGGSHFYVSDEAQNNGLIDAFGALTSGNTDLSQKSLQLESKGLT
LNSNAWMNDTVIIDSTVGKDTFFLITWNSLPPSISLWDPSGTIMENFTVDATSKMAYLSIPG
TAKVGTWAYNLQAKANPETLTITVTSRAANSSVPPITVNAKMNKDVNSFPSPMIVYAEILQG
YVPVLGANVTAFIESQNGHTEVLELLDNGAGADSFKNDGVYSRYFTAYTENGRYSLKVRAHG
GANTARLKLRPPLNRAAYIPGWVVNGEIEANPPRPEIDEDTQTTLEDFSRTASGGAFVVSQV
PSLPLPDQYPPSQITDLDATVHEDKIILTWTAPGDNFDVGKVQRYIIRISASILDLRDSFDD
ALQVNTTDLSPKEANSKESFAFKPENISEENATHIFIAIKSIDKSNLTSKVSNIAQVTLFIP
OANPDDIDPTPTPTPTPTPDKSHNSGVNISTLVLSVIGSVVIVNFILSTTI

Signal peptide:

amino acids 1-21

Putative transmembrane domains:

amino acids 284-300, 617-633

Leucine zipper pattern.

amino acids 469-491, 476-498

N-glycosylation site.

amino acids 20-24, 75-79, 340-344, 504-508, 542-546, 588-592, 628-632, 811-815, 832-836, 837-841, 852-856, 896-900

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FIGURE 275

GCCCCGGCTTTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCCTGAATGATGATGGTTCGCCGGGGGCTGCTTGCGTGGATTTCCCGGGTGGTGGTTTTTGCTGGTGCTCCTCTGCTGTGCTATCTCTGTCCTGTTACATGTTGGCCTGCACCCCAAAAGGTGACGAGGAGCAGCTGGCACTGCCCAGGGCCAACAGC CCTGTACATGTTGGCCTGCACCCCAAAAGGTGACGAGGAGCAGCTGGCACTGCCCAGGGCCAACAGC
CCCACGGGGAAGGAGGGGTACCAGGCCGTCCTTCAGAAGTTGGAGGAGCAGCACCGCAACTACGTGA
GCAGCCTGAAGCGGCAGATCGCACAGCTCAAGGAGGAGCTGCAGGAGGAGGAGCACCCCCAGAGAAAACCCAG
GCCGACCTCCTGGCCTTCCTGCACTCGCAGGTGGACAAGGCAGGAGGACCCCCCAGAGAAAACCCAG
CCCACAGAGTATGCAGCAGTGCCTTTCGATAGCTTTACTCTACAGAAGGTGATGCTGGAGACTGG
CCTTACCCGCCACCCCGAGGAGAAGCCTGTGAGGAAAGGGACAAGCGGATGAGTTGGTGGAAGCCATT
GAATCAGCCTTGGAGACCCTGAACAATCCTGCAGAGAAAGGGACAATCACCGTCCTTACACGGCCT
CTGATTTCATAGAAGGGACTTCACAGAAAGGGACAAAGGGACATTTTATTCAACACCTTCAA AGGGACCACAACAGGATTCAAACGCTCATCTTATTTCGACCATTCAGCCCCATCATGAAAGTG
AAAAATGAAAAGCTCAACATGGCCAACACGCTTATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGG
ACAAGTTCCGGCAGTTCATGCAGAATTCAGGGAGATGTGCATTGAGCAGGAGTGCCATCT
CACTGTTGTTTACTTTGGGAAAGAAGAAATAAATGAAGTCAAAGGAATACTTGAAAACACTTCCAAA GGCCATGACGAGGCATCCCACGGCCAGCTGGGCATGCTGGTGTTCAGGCACGAGATAGAGGCTCAC
CTTCGCAAACAGAAACAGAAGACAAGTAGCAAAAAAAACA<u>TGA</u>ACTCCCAGAGAAGGATTGTGGGAGA
CACTTTTTCTTTCCTTTTTGCAATTACTGAAAGTGGCTGCAACAGAGAAAAGACTTCCATAAAGGACG
ACAAAAGAATTGGACTGATGGGTCAGAGATGAGAGAAAGCCTCCGATTTCTCTCTGTTGGGCTTTTTAC
AACAGAAATCAAAATCTCCGCTTTGCCTGCAAAAGTAACCCAGTTGCACCCTGTGAAGTGTCTGACA
AAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTGTGGAGGTTTTTGAAATACACT
GAGACCTGTTGTTTTTGTGTGCTCATTGAAATATCATGATTTAAGAGCAGGCTCTAGTTTCTAGG
TAGCATGAAAGGCAAGCATATTTCTCCTCATATTGAATGACCTTATTTAAGATCACGTTCAGTACATTAAGACA GAGTATTTTCGAAGAGGAGCAACTGAACACTGGAGGAAAAGAAAATGACACTTTCTGCTTTACAGAA

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FIGURE 276

MMMVRRGLLAWISRVVVLLVLLCCAISVLYMLACTPKGDEEQLALPRANSPTGKEGYQAVLQ
EWEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADLLAFL
HSQVDKAEVNAGVKLATEYAAVPFDSFTLQKVYQLETGLTRHPEEKPVRKDKRDELVEAIES
ALETLNNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLILFRPFSPI
MKVKNEKLNMANTLINVIVPLAKRVDKFRQFMQNFREMCIEQDGRVHLTVVYFGKEEINEVK
GILENTSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVDIYFTSEFLNTCR
LNTQPGKKVFYPVLFSQYNPGIIYGHHDAVPPLEQQLVIKKETGFWRDFGFGMTCQYRSDFI
NIGGFDLDIKGWGGEDVHLYRKYLHSNLIVVRTPVRGLFHLWHEKRCMDELTPEQYKMCMQS
KAMNEASHGQLGMLVFRHEIEAHLRKQKQKTSSKKT

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FIGURE 277

GAAAGA**ATG**TTGTGGCTGCTCTTTTTTCTGGTGACTGCCATTCATGCTGAACTCTGTCAACC AGGTGCAGAAAATGCTTTTAAAGTGAGACTTAGTATCAGAACAGCTCTGGGAGATAAAGCAT ATGCCTGGGATACCAATGAAGAATACCTCTTCAAAGCGATGGTAGCTTTCTCCATGAGAAAA GTTCCCAACAGAGAAGCAACAGAAATTTCCCATGTCCTACTTTGCAATGTAACCCAGAGGGT ATCATTCTGGTTTGTGGTTACAGACCCTTCAAAAAATCACCCCTTCCTGCTGTTGAGGTGC CTGGAATTTTTAAAAATCCCTTCCACACTTGCACCACCCATGGACCCATCTGTGCCCATCTG GATTATTATATTTGGTGTGATATTTTGCATCATCATAGTTGCAATTGCACTACTGATTTTAT CAGGGATCTGGCAACGTAGAAGAAGAACAAAGAACCATCTGAAGTGGATGACGCTGAAGAT AAGTGTGAAAACATGATCACAATTGAAAATGGCATCCCCTCTGATCCCCTGGACATGAAGGG GGGCATATTAATGATGCCTTCATGACAGAGGATGAGAGGCTCACCCCTCTCTGAAGGGCTGT TGTTCTGCTTCCTCAAGAAATTAAACATTTGTTTCTGTGTGACTGCTGAGCATCCTGAAATA CCAAGAGCAGATCATATTTTGTTTCACCATTCTTCTTTTGTAATAAATTTTGAATGTGCT TGAAAGTGAAAAGCAATCAATTATACCCACCAACACCACTGAAATCATAAGCTATTCACGAC TCAAAATATTCTAAAATATTTTTCTGACAGTATAGTGTATAAATGTGGTCATGTGGTATTTG TAGTTATTGATTTAAGCATTTTTAGAAATAAGATCAGGCATATGTATATATTTTCACACTTC AAAGACCTAAGGAAAAATAAATTTTCCAGTGGAGAATACATATAATATGGTGTAGAAATCAT TGAAAATGGATCCTTTTTGACGATCACTTATATCACTCTGTATATGACTAAGTAAACAAAAG TGAGAAGTAATTATTGTAAATGGATGGATAAAAATGGAATTACTCATATACAGGGTGGAATT TTATCCTGTTATCACACCAACAGTTGATTATATATTTTCTGAATATCAGCCCCTAATAGGAC AATTCTATTGTTGACCATTTCTACAATTTGTAAAAGTCCAATCTGTGCTAACTTAATAAAG

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FIGURE 278

MLWLLFFLVTAIHAELCQPGAENAFKVRLSIRTALGDKAYAWDTNEEYLFKAMVAFSMRKVP NREATEISHVLLCNVTQRVSFWFVVTDPSKNHTLPAVEVQSAIRMNKNRINNAFFLNDQTLE FLKIPSTLAPPMDPSVPIWIIIFGVIFCIIIVAIALLILSGIWQRRRKNKEPSEVDDAEDKC ENMITIENGIPSDPLDMKGGILMMPS

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FIGURE 279

AACTCAAACTCCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCAGG GTGTTGGAGCCCTCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTCATG ATGGCAAGAGCTCTACTCGTGCGGTGCTTCTTCTCCTTGGCATACAGCTCACAGCTCTTTGG CCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTGCTGGAGGCTGTTAATGGGACAGATGC TCGGTTAAAATGCACTTTCTCCAGCTTTGCCCCTGTGGGTGATGCTCTAACAGTGACCTGGA ATTTTCGTCCTCTAGACGGGGGACCTGAGCAGTTTGTATTCTACTACCACATAGATCCCTTC CAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAATCCTGAGCGGTACGA TGCCTCCATCCTTCTCTGGAAACTGCAGTTCGACGACAATGGGACATACACCTGCCAGGTGA AGAACCCACCTGATGTTGATGGGGTGATAGGGGAGATCCGGCTCAGCGTCGTGCACACTGTA CGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCATTGGCTCTGCCTGTGCACTGATGATCAT AATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAAAAGCGATGGGCCGAAAGAGCTC ATAAAGTGGTGGAGATAAAATCAAAAGAAGAGGAAAGGCTCAACCAAGAGAAAAAGGTCTCT GTTTATTTAGAAGACACAGAC**TAA**CAATTTTAGATGGAAGCTGAGATGATTTCCAAGAACAA GAACCCTAGTATTTCTTGAAGTTAATGGAAACTTTTCTTTGGCTTTTTCCAGTTGTGACCCGT TTTCCAACCAGTTCTGCAGCATATTAGATTCTAGACAAGCAACACCCCTCTGGAGCCAGCAC AGTGCTCCTCCATATCACCAGTCATACACAGCCTCATTATTAAGGTCTTATTTAATTTCAGA GTGTAAATTTTTTCAAGTGCTCATTAGGTTTTATAAACAAGAAGCTACATTTTTGCCCTTAA GACACTACTTACAGTGTTATGACTTGTATACACATATATTGGTATCAAAGGGGATAAAAGCC AATTTGTCTGTTACATTTCCTTTCACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTA ATGTGTTTACTCTCTTCCCACATTCTCAATTAAAAGGTGAGCTAAGCCTCCTCGGTG TTTCTGATTAACAGTAAATCCTAAATTCAAACTGTTAAATGACATTTTTATTTTTTATGTCTC TTTGTCG

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FIGURE 280

MYGKSSTRAVLLLLGIQLTALWPIAAVEIYTSRVLEAVNGTDARLKCTFSSFAPVGDALTVT WNFRPLDGGPEQFVFYYHIDPFQPMSGRFKDRVSWDGNPERYDASILLWKLQFDDNGTYTCQ VKNPPDVDGVIGEIRLSVVHTVRFSEIHFLALAIGSACALMIIIVIVVVLFQHYRKKRWAER AHKVVEIKSKEEERLNQEKKVSVYLEDTD

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FIGURE 281

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FIGURE 282

MKFLAVLVLLGVSIFLVSAQNPTTAAPADTYPATGPADDEAPDAETTAAATTATTAAPTTAT
TAASTTARKDIPVLPKWVGDLPNGRVCP

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FIGURE 283

GGACTCTGAAGGTCCCAAGCAGCTGCTGAGGCCCCCAAGGAAGTGGTTCCAACCTTGGACCC
CTAGGGGTCTGGATTTGCTGGTTAACAAGATAACCTGAGGGCAGGACCCCATAGGGGAATGC
TACCTCCTGCCCTTCCACCTGCCCTGGTGTTCACGGTGGCCTGGTCCCTCCTTGCCGAGAGA
GTGTCCTGGGTCAGGGACGCAGAGGACGCTCACAGACTCCAGCCCTTTGTTACCGAGAGGAC
ACTTGGCAAGGTCCAGCGATGGTCCGGAGTCCACACACAGACTGCGGGCAGGGCAGGAGGGG
GACAGTTCTGTTGTGCTTGGTTGGACAGTAAGAGGGTCTTGGCCAGTCCAGGGTGGGGGGG
GCAAACTCCATAAAGAACCAGAGGGTCTGGGCCCCGGCCACAGAGTCATCTGCCCAGCTCCT
CTGCTGCTGGCCAGTGGGAGTGGCACGAGGTGGGGCTTTGTGCCAGTAAAAACCACAGGCTGG
ATTTGCCTGCGGGCCATGGTCCCTGTCTAGGGCAGCAATTCTCAACCTTCTTGCTCTCAGGA
CCCCAAAGAGCTTTCATTGTATCTATTGATTTTTACCACATTAGCAATTAAAACTGAGAAAT
GGGCCGGGCACGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGTGGAT
CACCTGAGATCAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCTTGTCTACTAAAAA
TACAAAAAATTAGCCAGGCACAGTGGTGCCCTGGTAGTCCCAGTTACTCGGGAGGCTGAG
GCAGGAAAATCGCTTGAACCCAGGAGGCGGACGTTGCGGTGAGCCGAGATCGCCCCCTGAT
TCCAGCCTGGCCACAAGAGTGAACCTCCATCTCACCA

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FIGURE 284

MLPPALPPALVFTVAWSLLAERVSWVRDAEDAHRLQPFVTERTLGKVQRWSGVHTQTGGRAG GGQFCCAWLDSKRVLASPGWGAANSIKNQRVWAPATESSAQLLCCWPVGVARGGALCQ

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FIGURE 285

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FIGURE 286

MPVPALCILWALAMVTRPASAAPMGGPELAQHEELTLIFHGTLQLGQALNGVYRTTEGRLTK ARNSLGLYGRTIELLGQEVSRGRDAAQELRASLLETQMEEDILQLQAEATAEVLGEVAQAQK VLRDSVQRLEVQLRSAWLGPAYREFEVLKAHADKQSHILWALTGHVQRQRREMVAQQHRLRQ IQERLHTAALPA

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FIGURE 287

GGCAACATGGCTCAGCAGGCTTGCCCCAGAGCCATGGCAAAGAATGGACTTGTAATTTGCAT CCTGGTGATCACCTTACTCCTGGACCAGACCACCAGCCACACATCCAGATTAAAAGCCAGGA AGCACAGCAAACGTCGAGTGAGAGACAAGGATGGAGATCTGAAGACTCAAATTGAAAAGCTC TAAAGTTCACAAGAAATGCTACCTTGCTTCAGAAGGTTTGAAGCATTTCCATGAGGCCAATG AAGACTGCATTTCCAAAGGAGGAATCCTGGTTATCCCCAGGAACTCCGACGAAATCAACGCC CTCCAAGACTATGGTAAAAGGAGCCTGCCAGGTGTCAATGACTTTTGGCTGGGCATCAATGA ACCGTGCACAGCCTAACGGTGGCAAGCGAGAAAACTGTGTCCTGTTCTCCCAATCAGCTCAG GGCAAGTGGAGTGATGAGGCCTGTCGCAGCAGCAAGAGATACATATGCGAGTTCACCATCCC TAAATAGGTCTTTCTCCAATGTGTCCTCCAAGCAAGATTCATCATAACTTATAGGTTCATGA TCTCTAAGATCAAGTAAAAATCATAATTTTTACTTATTAAAAAATTGCAACAAGATCAAT GTCCATAGCAATATGATAGCATCAGCCAATTTTGCTAACACATTTCTTTGGGATTTTGCCCT TCCTGGGGTATAGGGGATCAGAAATATTGATCCATGTGCACGCAGATAAAATGGCTTCTGCT TTCCCTTGGAAGTTTAGCGTATGTTTGACTAACAAAAATTCCCTACATCAGAGACTCTAGGT GCTATATAATCCAAAAACTTTTCAGCCTGTTGCTCATTCTGTCCCATGCTGGCAATAATACC TTGTCAGCCCATTACCCTTATTTTGAATTGCTCCATCTCCTGGTGGGACTTGTATCTTGTCT TACCCTTTTTTTGGAAGTTTCCAGCCGCAATTTGAAATGAAATGACAAGGTGTATATTTGAT CAATTTCATTCCCACCATTGCATTACAACCTCTAACTTAAATGGGTAACCCTAAGGCATAT AGCATCCTTACTCTCACCTTTTATGAGATTGAGAGTGGACTTACATTTCCTTTTTTACATTT TCGTATATTTATTTTTTTAGCCATCATTATATGTTTAAGTCTATTATGGGCAACCAATCTT TGGAAGCTGAAAACTGAATTTAAAGAATGCTATCTTGGAAAATTGCATACGTCTGTGCAATT TTTTATTCTGCCTAGTGCTATTCTGCTTGTTTAACTAGATTGTACAAAATAACTTCATTGCT TAATATCAAATTACAAAGTTTAGACTTGGAGGGAAATGGGCTTTTTAGAAGCAAACAATTTT AAATATATTTTGTTCTTCAAATAAATAGTGTTTTAAACATTGAATGTGTTTTGTGAACAATAT CCCACTTTGCAAACTTTAACTACACATGCTTGGAATTAAGTTTTTAGCTGTTTTCATTGCTCA

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FIGURE 288

MAQQACPRAMAKNGLVICILVITLLLDQTTSHTSRLKARKHSKRRVRDKDGDLKTQIEKLWT EVNALKEIQALQTVCLRGTKVHKKCYLASEGLKHFHEANEDCISKGGILVIPRNSDEINALQ DYGKRSLPGVNDFWLGINDMVTEGKFVDVNGIAISFLNWDRAQPNGGKRENCVLFSQSAQGK WSDEACRSSKRYICEFTIPK

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FIGURE 289

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FIGURE 290

MKLAALLGLCVALSCSSAAAFLVGSAKPVAQPVAALESAAEAGAGTLANPLGTLNPLKLLLS SLGIPVNHLIEGSQKCVAELGPQAVGAVKALKALLGALTVFG

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FIGURE 291

TGAAGGACTTTTCCAGGACCCAAGGCCACACACTGGAAGTCTTGCAGCTGAAGGGAGGCACT CCTTGGCCTCCGCAGCCGATCACATGAAGGTGGTGCCAAGTCTCCTGCTCTCCGTCCTCCTG GCACAGGTGTGGCTGGTACCCGGCTTGGCCCCCAGTCCTCAGTCGCCAGAGACCCCAGCCCC TCAGAACCAGACCAGCAGGGTAGTGCAGGCTCCCAGGGAAGAAGAAGATGAGCAGGAGG CCAGCGAGGAGAAGGCCGGTGAGGAAGAGAAGCCTGGCTGATGGCCAGCAGCAGCAGCTT GCCAAGGAGACTTCAAACTTCGGATTCAGCCTGCTGCGAAAGATCTCCATGAGGCACGATGG CAACATGGTCTTCTCCATTTGGCATGTCCTTGGCCATGACAGGCTTGATGCTGGGGGCCA CAGGGCCGACTGAAACCCAGATCAAGAGGGGCTCCACTTGCAGGCCCTGAAGCCCACCAAG CCCGGGCTCCTGCCTTTTAAGGGACTCAGAGAGCCCTCTCCCGCAACCTGGAACT GGGCCTCTCACAGGGGAGTTTTGCCTTCATCCACAAGGATTTTGATGTCAAAGAGACTTTCT TCAATTTATCCAAGAGGTATTTTGATACAGAGTGCGTGCCTATGAATTTTCGCAATGCCTCA CAGGCCAAAAGGCTCATGAATCATTACATTAACAAAGAGACTCGGGGGAAAATTCCCAAACT GTTTGATGAGATTAATCCTGAAACCAAATTAATTCTTGTGGATTACATCTTGTTCAAAGGGA AATGGTTGACCCCATTTGACCCTGTCTTCACCGAAGTCGACACTTTCCACCTGGACAAGTAC AAGACCATTAAGGTGCCCATGATGTACGGTGCAGGCAAGTTTGCCTCCACCTTTGACAAGAA TTTTCGTTGTCATGTCCTCAAACTGCCCTACCAAGGAAATGCCACCATGCTGGTGGTCCTCA TGGAGAAAATGGGTGACCACCTCGCCCTTGAAGACTACCTGACCACAGACTTGGTGGAGACA GAAGTATGAGATGCATGAGCTGCTTAGGCAGATGGGAATCAGAAGAATCTTCTCACCCTTTG CTGACCTTAGTGAACTCTCAGCTACTGGAAGAATCTCCAAGTATCCAGGGTTTTACGAAGA ACAGTGATTGAAGTTGAAAGGGGCACTGAGGCAGTGGCAGGAATCTTGTCAGAAATTAC TGCTTATTCCATGCCTCCTGTCATCAAAGTGGACCGGCCATTTCATTTCATGATCTATGAAG AAACCTCTGGAATGCTTCTGTTTCTGGGCAGGGTGGTGAATCCGACTCTCCTA**TAA**TTCAGG TACCAGCAATGGATGGCAGGGGAGAGTGTTCCTTTTGTTCTTAACTAGTTTAGGGTGTTCTC AAATAAATACAGTAGTCCCCACTTATCTGAGGGGGGATACATTCAAAGACCCCCAGCAGATGC AAAGTTTAATTTATAAATTAGGCACAGTAAGAGATTAACAATAATAACAACATTAAGTAAAA TGAGTTACTTGAACGCAAGCACTGCAATACCATAACAGTCAAACTGATTATAGAGAAGGCTA CTAAGTGACTCATGGGCGAGGAGCATAGACAGTGTGGAGACATTGGGCCAAGGGGAGAATTCA CATCCTGGGTGGGACAGAGCAGGACGATGCAAGATTCCATCCCACTACTCAGAATGGCATGC TGCTTAAGACTTTTAGATTGTTTATTTCTGGAATTTTTCATTTAATGTTTTTTGGACCATGGT TGACCATGGTTAACTGAGACTGCAGAAAGCAAAACCATGGATAAGGGAGGACTACTACAAAA

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FIGURE 292

MKVVPSLLLSVLLAQVWLVPGLAPSPQSPETPAPQNQTSRVVQAPREEEEDEQEASEEKAGE
EEKAWLMASRQQLAKETSNFGFSLLRKISMRHDGNMVFSPFGMSLAMTGLMLGATGPTETQI
KRGLHLQALKPTKPGLLPSLFKGLRETLSRNLELGLSQGSFAFIHKDFDVKETFFNLSKRYF
DTECVPMNFRNASQAKRLMNHYINKETRGKIPKLFDEINPETKLILVDYILFKGKWLTPFDP
VFTEVDTFHLDKYKTIKVPMMYGAGKFASTFDKNFRCHVLKLPYQGNATMLVVLMEKMGDHL
ALEDYLTTDLVETWLRNMKTRNMEVFFPKFKLDQKYEMHELLRQMGIRRIFSPFADLSELSA
TGRNLQVSRVLRRTVIEVDERGTEAVAGILSEITAYSMPPVIKVDRPFHFMIYEETSGMLLF
LGRVVNPTLL

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FIGURE 293

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FIGURE 294

MRRLLLVTSLVVVLLWEAGAVPAPKVPIKMQVKHWPSEQDPEKAWGARVVEPPEKDDQLVVL FPVQKPKLLTTEEKPRGQGRGPILPGTKAWMETEDTLGRVLSPEPDHDSLYHPPPEEDQGEE RPRLWVMPNHQVLLGPEEDQDHIYHPQ

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FIGURE 295

TACCCAAGGAAAGTGCAGCTGAGACTCAGACAAGATTACAATGAACCAACTCAGCTTCCTGC TGGACCTGTTCTTCGTCTCCATCTCTGCCCAGAAGCTGCAAGGAAATCAAAGACGAATGTCC TAGTGCATTTGATGGCCTGTATTTTCTCCGCACTGAGAATGGTGTTATCTACCAGACCTTCT GTGACATGACCTCTGGGGGTGGCGGCTGGACCCTGGTGGCCAGCGTGCATGAGAATGACATG CGTGGGAAGTGCACGGTGGGCGATCGCTGGTCCAGTCAGCAGGGCAGCAAAGCAGACTACCC AGAGGGGGACGCAACTGGGCCAACTACAACACCTTTGGATCTGCAGAGGCGGCCACGAGCG ATGACTACAAGAACCCTGGCTACTACGACATCCAGGCCAAGGACCTGGGCATCTGGCACGTG CCCAATAAGTCCCCCATGCAGCACTGGAGAAACAGCTCCCTGCTGAGGTACCGCACGGACAC TGGCTTCCTCCAGACACTGGGACATAATCTGTTTGGCATCTACCAGAAATATCCAGTGAAAT ATGGAGAAGGAAAGTGTTGGACTGACAACGGCCCGGTGATCCCTGTGGTCTATGATTTTGGC GACGCCCAGAAAACAGCATCTTATTACTCACCCTATGGCCAGCGGGAATTCACTGCGGGATT TGTTCAGTTCAGGGTATTTAATAACGAGAGCAGCCAACGCCTTGTGTGCTGGAATGAGGG TCACCGGATGTAACACTGAGCATCACTGCATTGGTGGAGGAGGATACTTTCCAGAGGCCAGT CCCCAGCAGTGTGGAGATTTTTCTGGTTTTGATTGGAGTGGATATGGAACTCATGTTGGTTA CAGCAGCAGCCGTGAGATAACTGAGGCAGCTGTGCTTCTATTCTATCGT**TGA**GAGTTTTGTG GGAGGGAACCCAGACCTCTCCCCAACCATGAGATCCCAAGGATGGAGAACAACTTACCCA GTAGCTAGAATGTTAATGGCAGAAGAGAAAACAATAAATCATATTGACTCAAGAAAAAAA

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FIGURE 296

MNQLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRTEN GVIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRWSSQQGSKADYPEGDGNWANYNTFG SAEAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLLRYRTDTGFLQTLGHNLFGI YQKYPVKYGEGKCWTDNGPVIPVVYDFGDAQKTASYYSPYGQREFTAGFVQFRVFNNERAAN ALCAGMRVTGCNTEHHCIGGGGYFPEASPQQCGDFSGFDWSGYGTHVGYSSSREITEAAVLL FYR

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FIGURE 297

GCGGAGCCGGCCGGCTGCGCAGAGGAGCCGCTCTCGCCGCCGCCACCTCGGCTGGGAGCC CACGAGGCTGCCGCATCCTGCCCTCGGAACAATGGGACTCGGCGCGAGGTGCTTGGGCCG CGCTGCTCCTGGGGACGCTGCAGGTGCTAGCGCTGCTGGGGGCCCCCATGAAAGCGCAGCC ATGGCGGCATCTGCAAACATAGAGAATTCTGGGCTTCCACACAACTCCAGTGCTAACTCAAC AGAGACTCTCCAACATGTGCCTTCTGACCATACAAATGAAACTTCCAACAGTACTGTGAAAC CACCAACTTCAGTTGCCTCAGACTCCAGTAATACAACGGTCACCACCATGAAACCTACAGCG GCATCTAATACAACACCAGGGATGGTCTCAACAAATATGACTTCTACCACCTTAAAGTC TACACCCAAAACAACAAGTGTTTCACAGAACACATCTCAGATATCAACATCCACAATGACCG TAACCCACAATAGTTCAGTGACATCTGCTGCTTCATCAGTAACAATCACAACAACTATGCAT .TCTGAAGCAAAGAAAGGATCAAAATTTGATACTGGGAGCTTTGTTGGTGGTATTGTATTAAC GCTGGGAGTTTTATCTATTCTTTACATTGGATGCAAAATGTATTACTCAAGAAGAGGCATTC GGTATCGAACCATAGATGAACATGATGCCATCATT**TAA**GGAAATCCATGGACCAAGGATGGA ATACAGATTGATGCTGCCCTATCAATTAATTTTGGTTTATTAATAGTTTAAAAACAATATTCT CTTTTTGAAAATAGTATAAACAGGCCATGCATATAATGTACAGTGTATTACGTAAATATGTA AAGATTCTTCAAGGTAACAAGGGTTTGGGGTTTTGAAATAAACATCTGGATCTTATAGACCGT GGGGTGGGGCATTGGTCACATATGACCAGTAATTGAAAGACGTCATCACTGAAAGACAGAA TGCCATCTGGGCATACAAATAAGAAGTTTGTCACAGCACTCAGGATTTTGGGTATCTTTTGT AGCTCACATAAAGAACTTCAGTGCTTTTCAGAGCTGGATATATCTTAATTACTAATGCCACA CAGAAATTATACAATCAAACTAGATCTGAAGCATAATTTAAGAAAAACATCAACATTTTTTG TGCTTTAAACTGTAGTAGTTGGTCTAGAAACAAAATACTCC

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FIGURE 298

MGLGARGAWAALLLGTLQVLALLGAAHESAAMAASANIENSGLPHNSSANSTETLQHVPSDH TNETSNSTVKPPTSVASDSSNTTVTTMKPTAASNTTTPGMVSTNMTSTTLKSTPKTTSVSQN TSQISTSTMTVTHNSSVTSAASSVTITTTMHSEAKKGSKFDTGSFVGGIVLTLGVLSILYIG CKMYYSRRGIRYRTIDEHDAII

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FIGURE 299

CAGCCGGGTCCCAAGCCTGTGCCTGAGCCTGAGCCTGAGCCCGAGCCGGGAGCCGG TCGCGGGGGCTCCGGGCTGTGGGACCGCTGGGCCCCCAGCGATGGCGACCCTGTGGGGAGGC ATAAAGAAAATTCTGGGCATATTTATAATAAGAACATATCTCAGAAAGATTGTGATTGCCTT CATGTTGTGGAGCCCATGCCTGTGCGGGGGCCTGATGTAGAAGCATACTGTCTACGCTGTGA ATGCAAATATGAAGAAGAAGCTCTGTCACAATCAAGGTTACCATTATAATTTATCTCTCCA TTTTGGGCCTTCTACTTCTGTACATGGTATATCTTACTCTGGTTGAGCCCATACTGAAGAGG CGCCTCTTTGGACATGCACAGTTGATACAGAGTGATGATGATATTGGGGATCACCAGCCTTT TGCAAATGCACACGATGTGCTAGCCCGCTCCCGCAGTCGAGCCAACGTGCTGAACAAGGTAG CTGGAAAGAACTGACTGGGTTTTGCTGGGTTTCATTTTAATACCTTGTTGATTTCACCAACT ATAATAGAGACATTTTTAAAAGCACACAGCTCAAAGTCAGCCAATAAGTCTTTTCCTATTTG TGACTTTTACTAATAAAATAAATCTGCCTGTAAATTATCTTGAAGTCCTTTACCTGGAACA AGCACTCTCTTTTTCACCACATAGTTTTAACTTGACTTTCAAGATAATTTTCAGGGTTTTTG TTGTTGTTGTTTTGTTTGTTTTGGTGGGAGGGGAGGGGATGCCTGGGAAGTGGTT AACAACTTTTTTCAAGTCACTTTACTAAACAAACTTTTGTAAATAGACCTTACCTTCTATTT TCGAGTTTCATTTATATTTTGCAGTGTAGCCAGCCTCATCAAAGAGCTGACTTACTCATTTG ACTTTTGCACTGACTGTATTATCTGGGTATCTGCTGTGTCTGCACTTCATGGTAAACGGGAT CTAAAATGCCTGGTGGCTTTTCACAAAAAGCAGATTTTCTTCATGTACTGTGATGTCTGATG CAATGCATCCTAGAACAAACTGGCCATTTGCTAGTTTACTCTAAAGACTAAACATAGTCTTG GTGTGTGTGTCTTACTCATCTTCTAGTACCTTTAAGGACAAATCCTAAGGACTTGGACACT TGCAATAAAGAAATTTTATTTTAAACCCAAGCCTCCCTGGATTGATAATATACACATTTG TCAGCATTTCCGGTCGTGGTGAGAGGCAGCTGTTTGAGCTCCAATATGTGCAGCTTTGAACT AGGGCTGGGGTTGTGGGTGCCTCTTCTGAAAGGTCTAACCATTATTGGATAACTGGCTTTTT TCTTCCTATGTCCTCTTTGGAATGTAACAATAAAAATAATTTTTGAAACATCAA

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FIGURE 300

MATLWGGLLRLGSLLSLSCLALSVLLLAQLSDAAKNFEDVRCKCICPPYKENSGHIYNKNIS QKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLLLYMVYLTL VEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVEYAQQRWKLQVQEQ RKSVFDRHVVLS

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FIGURE 301

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FIGURE 302

MAYSTVQRVALASGLVLALSLLLPKAFLSRGKRQEPPPTPEGKLGRFPPMMHHHQAPSDGQT PGARFQRSHLAEAFAKAKGSGGGAGGGGSGRGLMGQIIPIYGFGIFLYILYILFKVSRIILI ILHQ

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FIGURE 303

CGGCTCGAGTGCAGCTGTGGGGAGATTTCAGTGCATTGCCTCCCTGGGTGCTCTTCATCTT GGATTTGAAAGTTGAGAGCAGCATGTTTTGCCCACTGAAACTCATCCTGCTGCCAGTGTTAC TGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTCCATGTG GGTGATTCAGCTCTGATGGGATGTTTTTCCAGAGCACAGAAGACAAATGTATATTCAAGAT AGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGATATGTGCTATACTATTACTCCA ATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGGGACATCTTATGC AATGATGGCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGAACCTATATCTGTGA AATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTACTGCATGTGCTTCCAG AGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTTTCAGGACGCGCGCAAAGGA GGAGATTGTATTTCGTTACTACCACAAACTCAGGATGTCTGTGGAGTACTCCCAGAGCTGGG GCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATTTTCCGCAATGACGGTTCCATCATG CTTCAAGGAGTGAGGGAGTCAGATGGAGGAAACTACACCTGCAGTATCCACCTAGGGAACCT GGTGTTCAAGAAAACCATTGTGCTGCATGTCAGCCCGGAAGAGCCTCGAACACTGGTGACCC CGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGTAATCAGTTGGTGATCATTGTGGGAATTGTC TGTGCCACAATCCTGCTGCTCCCTGTTCTGATATTGATCGTGAAGAAGACCTGTGGAAATAA GAGTTCAGTGAATTCTACAGTCTTGGTGAAGAACACGAAGAAGACTAATCCAGAGATAAAAG AAAAACCCTGCCATTTTGAAAGATGTGAAGGGGAGAAACACATTTACTCCCCAATAATTGTA CGGGAGGTGATCGAGGAAGAAGAACCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCA CCCAGTTTGGCCTTCTCTGAGGTCAGATCGGAACAACTCACTTGAAAAAAAGTCAGGTGGGG GAATGCCAAAAACACAGCAAGCCTTT<u>TGA</u>GAAGAATGGAGAGTCCCTTCATCTCAGCAGCGG TGGAGACTCTCTCTGTGTGTGTCCTGGGCCACTCTACCAGTGATTTCAGACTCCCGCTCTC CCAGCTGTCCTCTCTCTCTTTTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGG CAGAGAGACTGGACAGCTCTGGAGGAACAGGCCTGCTGAGGGGGAGGGGGAGCATGGACTTGGC CTCTGGAGTGGGACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCGTT GGATCAGACCCTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATA AAAACCAACCCAAATCAA

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FIGURE 304

MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLSPG
EHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRLKGES
QVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEIVFRYY
HKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGNLVFKKTIV
LHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTCGNKSSVNSTV
LVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEATYMTMHPVWPSLR
SDRNNSLEKKSGGGMPKTQQAF

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FIGURE 305

CTATGAAGAAGCTTCCTGGAAAACAATAAGCAAAGGAAAACAAATGTGTCCCATCTCACATG GTTCTACCCTACTAAAGACAGGAAGATCATAAACTGACAGATACTGAAATTGTAAGAGTTGG AAACTACATTTTGCAAAGTCATTGAACTCTGAGCTCAGTTGCAGTACTCGGGAAGCC**ATG**CA GGATGAAGATGGATACATCACCTTAAATATTAAAACTCGGAAACCAGCTCTCGTCTCCGTTG GCCCTGCATCCTCCTGGTGGCGTGTGATGGCTTTGATTCTGCTGATCCTGTGCGTGGGG ATGGTTGTCGGGCTGGTGGCTCTGGGGATTTGGTCTGTCATGCAGCGCAATTACCTACAAGA TGAGAATGAAAATCGCACAGGAACTCTGCAACAATTAGCAAAGCGCTTCTGTCAATATGTGG TAAAACAATCAGAACTAAAGGGCACTTTCAAAGGTCATAAATGCAGCCCCTGTGACACAAAC TGGAGATATTATGGAGATAGCTGCTATGGGTTCTTCAGGCACAACTTAACATGGGAAGAGAG TAAGCAGTACTGCACTGACATGAATGCTACTCTCCTGAAGATTGACAACCGGAACATTGTGG AGTACATCAAAGCCAGGACTCATTTAATTCGTTGGGTCGGATTATCTCGCCAGAAGTCGAAT GAGGTCTGGAAGTGGGAGGATGGCTCGGTTATCTCAGAAAATATGTTTGAGTTTTTGGAAGA TGGAAAAGGAAATATGAATTGTGCTTATTTTCATAATGGGAAAATGCACCCTACCTTCTGTG AGAACAAACATTATTTAATGTGTGAGAGGAAGGCTGGCATGACCAAGGTGGACCAACTACCT **TAA**TGCAAAGAGGTGGACAGGATAACACAGATAAGGGCTTTATTGTACAATAAAAGATATGT ATGAATGCATCAGTAGCTGAAAAAAAAAAAAAA

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FIGURE 306

MQDEDGYITLNIKTRKPALVSVGPASSSWWRVMALILLILCVGMVVGLVALGIWSVMQRNYL QDENENRTGTLQQLAKRFCQYVVKQSELKGTFKGHKCSPCDTNWRYYGDSCYGFFRHNLTWE ESKQYCTDMNATLLKIDNRNIVEYIKARTHLIRWVGLSRQKSNEVWKWEDGSVISENMFEFL EDGKGNMNCAYFHNGKMHPTFCENKHYLMCERKAGMTKVDQLP

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FIGURE 307

CCCACGCGTCCGCGCAGTCGCGCAGTTCTGCCTCCGCCTGCCAGTCTCGCCCGCGATCCCGG CCCGGGGCTGTGGCGTCGACTCCGACCCAGGCAGCCAGCAGCCCGCGCGGGAGCCGGACCGC CGCCGGAGGACCCCGACGCATGCTGAGCCCCCTCCTTTGCTGAAGCCCGAGTGCGGAGAA GCCCGGGCAAACGCAGGCTAAGGAGACCAAAGCGGCGAAGTCGCGAGACAGCGGACAAGCAG CGTCGTGGCCATGCCGGCGGCTATCGCCAGCTCGCTCATCCGTCAGAAGAGGCAAGCCCGCG AGCGCGAGAAATCCAACGCCTGCAAGTGTGTCAGCAGCCCCAGCAAAGGCAAGACCAGCTGC GACAAAAACAAGTTAAATGTCTTTTCCCGGGTCAAACTCTTCGGCTCCAAGAAGAGGCGCAG AAGAAGACCAGAGCCTCAGCTTAAGGGTATAGTTACCAAGCTATACAGCCGACAAGGCTACC ACTTGCAGCTGCAGGCGGATGGAACCATTGATGGCACCAAAGATGAGGACAGCACTTACACT CTGTTTAACCTCATCCCTGTGGGTCTGCGAGTGGTGGCTATCCAAGGAGTTCAAACCAAGCT GTACTTGGCAATGAACAGTGAGGGATACTTGTACACCTCGGAACTTTTCACACCTGAGTGCA AATTCAAAGAATCAGTGTTTGAAAATTATTATGTGACATATTCATCAATGATATACCGTCAG CAGCAGTCAGGCCGAGGGTGGTATCTGGGTCTGAACAAAGAAGGAGAGATCATGAAAGGCAA CCATGTGAAGAAGAACAAGCCTGCAGCTCATTTTCTGCCTAAACCACTGAAAGTGGCCATGT ACAAGGAGCCATCACTGCACGATCTCACGGAGTTCTCCCGATCTGGAAGCGGGACCCCAACC AAGAGCAGAAGTGTCTCTGGCGTGCTGAACGGAGGCAAATCCATGAGCCACAATGAATCAAC **GTAG**CCAGTGAGGGCAAAAGAAGGGCTCTGTAACAGAACCTTACCTCCAGGTGCTGTTGAAT CAGAGTTCACTATTCTATCTGCCATTAGACCTTCTTATCATCCATACTAAAGC

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FIGURE 308

></usr/seqdb2/sst/DNA/Dnaseqs.full/ss.DNA28498

><subunit 1 of 1, 245 aa, 1 stop

><MW: 27564, pI: 10.18, NX(S/T): 1

MAAAIASSLIRQKRQAREREKSNACKCVSSPSKGKTSCDKNKLNVFSRVKLFGSKKRRRRP EPQLKGIVTKLYSRQGYHLQLQADGTIDGTKDEDSTYTLFNLIPVGLRVVAIQGVQTKLYLA MNSEGYLYTSELFTPECKFKESVFENYYVTYSSMIYRQQQSGRGWYLGLNKEGEIMKGNHVK KNKPAAHFLPKPLKVAMYKEPSLHDLTEFSRSGSGTPTKSRSVSGVLNGGKSMSHNEST

N-glycosylation site.

amino acids 242-246

Glycosaminoglycan attachment site.

amino acids 165-169, 218-222

Tyrosine kinase phosphorylation site.

amino acids 93-100

N-myristoylation site.

amino acids 87-93, 231-237

ATP/GTP-binding site motif A (P-loop).

amino acids 231-239

HBGF/FGF family proteins

amino acids 78-94, 102-153

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FIGURE 309

CCAGGATGGAGCTGGGGCCTGTATAGCCATATTATTGTTCTATGCTACTAGACATGGGGGGG ACTTGGTGAAAAAGGTATTATCCAGCCAGAGGGTCTGGGAGCCCTGTCTTACTGAACCTGGG CAACCTGGATATTCTGAGACATATTTTGGGGGGGATTTCAGTGAAAAAAGTGGGGGATCCCCT CCCCAGTAGGGGTGGGATGAGCGAATATTCCCAAAGCTAAAGTCCCACACCCTGTAGATTAC AAGAGTGGATTTGGCAGGAGTGTGCCCCAAAATACAGTGGAAAGGTGCCTGAAGATATTTAA GAGAGGAGGGAAAGGGGACGTTTTCAATAGGAGGCAAAACTCGAGGGTGGGATCCACTGAGG AGTACATAGGCTGCTGGATCTGGTGGAGCCAGCACTGGGCCCACGGGTGGTAACTGGCTGCT CGAGTCGGGGCCTGAGCGTCAAGAGCATGCCCTAGTGAGCGGGCTCCTCTGGGGGAGCCCAG CGCGCTCCGGGCGCCTGCCGGTTTGGGGGTGTCTCCTCCCGGGGCGCTATGGCGGCGCTGGC CGCAGCGGCGCGTGTGTCCCCGCGGCACCAAGTCCCTTTGCCAGAAGCAGCTCCTCATCCTG CTGTCCAAGGTGCGACTGTGCGGGGGGGCGGCCCGCGCGGGCCGGACCGCGGGCCCGGAGCCTCA GCTCAAAGGCATCGTCACCAAACTGTTCTGCCGCCAGGGTTTCTACCTCCAGGCGAATCCCG ACGGAAGCATCCAGGGCACCCCAGAGGATACCAGCTCCTTCACCCACTTCAACCTGATCCCT GTGGGCCTCCGTGTGGTCACCATCCAGAGCGCCAAGCTGGGTCACTACATGGCCATGAATGC TGAGGGACTGCTCTACAGTTCGCCGCATTTCACAGCTGAGTGTCGCTTTAAGGAGTGTGTCT TTGAGAATTACTACGTCCTGTACGCCTCTGCTCTACCGCCAGCGTCGTTCTGGCCGGGCC TGGTACCTCGGCCTGGACAAGGAGGGCCAGGTCATGAAGGGAAACCGAGTTAAGAAGACCAA GGCAGCTGCCCACTTTCTGCCCAAGCTCCTGGAGGTGGCCATGTACCAGGAGCCTTCTCTCC ACAGTGTCCCCGAGGCCTCCCCTTCCAGTCCCCCTGCCCCCTGAAATGTAGTCCCTGGACTG GAGGTTCCCTGCACTCCCAGTGAGCCAGCCACCACCACCACCTGT

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FIGURE 310

MAALASSLIRQKREVREPGGSRPVSAQRRVCPRGTKSLCQKQLLILLSKVRLCGGRPARPDR GPEPQLKGIVTKLFCRQGFYLQANPDGSIQGTPEDTSSFTHFNLIPVGLRVVTIQSAKLGHY MAMNAEGLLYSSPHFTAECRFKECVFENYYVLYASALYRQRRSGRAWYLGLDKEGQVMKGNR VKKTKAAAHFLPKLLEVAMYQEPSLHSVPEASPSSPPAP

Tyrosine kinase phosphorylation site:

amino acids 199-207

N-myristoylation sites:

amino acids 54-60, 89-95, 131-137

HBGF/FGF family signature:

amino acids 131-155

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FIGURE 311

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FIGURE 312

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA28503</pre>

><subunit 1 of 1, 247 aa; 1 stop

><MW: 27702, pI: 10.36, NX(S/T): 2

MAAAIASGLIRQKRQAREQHWDRPSASRRRSSPSKNRGLCNGNLVDIFSKVRIFGLKKRRLR RQDPQLKGIVTRLYCRQGYYLQMHPDGALDGTKDDSTNSTLFNLIPVGLRVVAIQGVKTGLY IAMNGEGYLYPSELFTPECKFKESVFENYYVIYSSMLYRQQESGRAWFLGLNKEGQAMKGNR VKKTKPAAHFLPKPLEVAMYREPSLHDVGETVPKPGVTPSKSTSASAIMNGGKPVNKSKTT

N-glycosylation site.

amino acids 100-104, 242-246

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 28-32, 29-33

Tyrosine kinase phosphorylation site.

amino acids 199-207

N-myristoylation site.

amino acids 38-44, 89-95, 118-124, 122-128, 222-228

HBGF/FGF family proteins.

amino acids 104-155, 171-198

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FIGURE 313

ACGAAGCTTTTTCTTGTGAGCCCTGGATCTTAACACAAATGTGTATATGTGCACACAGGGAGCATTCAAGAATG CTCCCCACCCCAAAAAAAAGGATGATTGGAAATGAAGAACCGAGGATTCACAAAGAAAAAGTATGTTCATTT TTCTCTATAAAGGAGAAAGTGAGCCAAGGAGATATTTTTGGAATGAAAAGTTTGGGGCCTTTTTTAGTAAAGTAA AGAACTGGTGTGGTGTTTTCCTTTCTTTTTGAATTTCCCACAAGAGGGAGAATTAATAATACATCTGC CAGTTGGATTTGTGCCTATGTTGACTAAAATTGACGGATAATTGCAGTTGGATTTTTCTTCATCAACCTCCTTT TTTTTAAATTTTTATTCCTTTTGGTATCAAGATCATGCGTTTTCTCTTGTTCTTAACCACCTGGATTTCCATCT GGATGTTGCTGTGATCAGTCTGAAATACAACTGTTTGAATTCCAGAAGGACCAACACCAGATAAATTATGA**ATG** TTGAACAAGATGACCTTACATCCACAGCAGATAATGATAGGTCCTAGGTTTAACAGGGCCCTATTTGACCCCCT GCTTGTGGTGCTGCTGCTCTTCAACTTCTTGTGGTGGCTGGTTGTGGTGCGGGCTCAGACCTGCCCTTCTGTGT GCTCCTGCAGCAACCAGTTCAGCAAGGTGATTTGTGTTCGGAAAAACCTGCGTGAGGTTCCGGATGGCATCTCC ACCAACACGGCTGCTGAACCTCCATGAGAACCAAATCCAGATCATCAAAGTGAACAGCTTCAAGCACTTGAG GCACTTGGAAATCCTACAGTTGAGTAGGAACCATATCAGAACCATTGAAATTGGGGCTTTCAATGGTCTGGCGA ACCTCAACACTCTGGAACTCTTTGACAATCGTCTTACTACCATCCCGAATGGAGCTTTTGTATACTTGTCTAAA CTGAAGGAGCTCTGGTTGCGAAACAACCCCATTGAAAGCATCCCTTCTTATGCTTTTAACAGAATTCCTTCTTT GCGCCGACTAGACTTAGGGGAATTGAAAAGACTTTCATACATCTCAGAAGGTGCCTTTGAAGGTCTGTCCAACT TGAGGTATTTGAACCTTGCCATGTGCAACCTTCGGGAAATCCCTAACCTCACACCGCTCATAAAACTAGATGAG CTGGATCTTTCTGGGAATCATTTATCTGCCATCAGGCCTGGCTCTTTCCAGGGTTTGATGCACCTTCAAAAACT GTGGATGATACAGTCCCAGATTCAAGTGATTGAACGGAATGCCTTTGACAACCTTCAGTCACTAGTGGAGATCA ACCTGGCACACAATAATCTAACATTACTGCCTCATGACCTCTTCACTCCCTTGCATCATCTAGAGCGGATACAT TTACATCACAACCCTTGGAACTGTAACTGTGACATACTGTGGCTCAGCTGGTGGATAAAAGACATGGCCCCCTC GAACACAGCTTGTTGTGCCCGGTGTAACACTCCTCCCAATCTAAAGGGGAGGTACATTGGAGAGCTCGACCAGA ATTACTTCACATGCTATGCTCCGGTGATTGTGGAGCCCCCTGCAGACCTCAATGTCACTGAAGGCATGGCAGCT GAGCTGAAATGTCGGGCCTCCACATCCCTGACATCTGTATCTTGGATTACTCCAAATGGAACAGTCATGACACA TGGGGCGTACAAAGTGCGGATAGCTGTGCTCAGTGATGGTACGTTAAATTTCACAAATGTAACTGTGCAAGATA CAGGCATGTACACATGTATGGTGAGTAATTCCGTTGGGAATACTACTGCTTCAGCCACCCTGAATGTTACTGCA GCAACCACTACTCCTTTCTCTTACTTTTCAACCGTCACAGTAGAGACTATGGAACCGTCTCAGGATGAGGCACG GACCACAGATAACAATGTGGGTCCCACTCCAGTGGTCGACTGGGAGACCACCAATGTGACCACCTCTCTCACAC CACAGAGCACAAGGTCGACAGAGAAAACCTTCACCATCCCAGTGACTGATATAAACAGTGGGATCCCAGGAATT GATGAGGTCATGAAGACTACCAAAATCATCATTGGGTGTTTTGTGGCCATCACACTCATGGCTGCAGTGATGCT GGTCATTTCTACAAGATGAGGAAGCAGCACCATCGGCAAAAACCATCACGCCCCAACAAGGACTGTTGAAATTA TTAATGTGGATGATGAGATTACGGGAGACACCCCATGGAAAGCCACCTGCCCATGCCTGCTATCGAGCATGAG CAGTTCAGTGCATGAACCGTTATTGATCCGAATGAACTCTAAAGACAATGTACAAGAGACTCAAATC<u>TAA</u>AACA TTTACAGAGTTACAAAAAACAATCAAAAAAAAAAAGACAGTTTATTAAAAATGACACAAATGACTGGGCTAA TGATCTAAAGCAGACAAAA

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FIGURE 314

MLNKMTLHPQQIMIGPRFNRALFDPLLVVLLALQLLVVAGLVRAQTCPSVCSCSNQFSKVIC
VRKNLREVPDGISTNTRLLNLHENQIQIIKVNSFKHLRHLEILQLSRNHIRTIEIGAFNGLA
NLNTLELFDNRLTTIPNGAFVYLSKLKELWLRNNPIESIPSYAFNRIPSLRRLDLGELKRLS
YISEGAFEGLSNLRYLNLAMCNLREIPNLTPLIKLDELDLSGNHLSAIRPGSFQGLMHLQKL
WMIQSQIQVIERNAFDNLQSLVEINLAHNNLTLLPHDLFTPLHHLERIHLHHNPWNCNCDIL
WLSWWIKDMAPSNTACCARCNTPPNLKGRYIGELDQNYFTCYAPVIVEPPADLNVTEGMAAE
LKCRASTSLTSVSWITPNGTVMTHGAYKVRIAVLSDGTLNFTNVTVQDTGMYTCMVSNSVGN
TTASATLNVTAATTTPFSYFSTVTVETMEPSQDEARTTDNNVGPTPVVDWETTNVTTSLTPQ
STRSTEKTFTIPVTDINSGIPGIDEVMKTTKIIIGCFVAITLMAAVMLVIFYKMRKQHHRQN
HHAPTRTVEIINVDDEITGDTPMESHLPMPAIEHEHLNHYNSYKSPFNHTTTVNTINSIHSS
VHEPLLIRMNSKDNVQETQI

Signal sequence:

amino acids 1-44

Transmembrane domain:

amino acids 523-543

N-glycosylation site.

amino acids 278-282, 364-368, 390-394, 412-416, 415-419, 434-438, 442-446, 488-492, 606-610

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 183-187

Casein kinase II phosphorylation site.

amino acids 268-272, 417-421, 465-469, 579-583, 620-624

N-myristoylation site.

amino acids 40-46, 73-79, 118-124, 191-197, 228-234, 237-243, 391-397, 422-428, 433-439, 531-537

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FIGURE 315

GGCTGCAGCCACCTCGCGCGCACCCCGAGGCGCCCCAGCTCGCCCGAGGTCCGTCGGA GGCGCCCGGCCCCCGGAGCCAAGCAGCAACTGAGCGGGGAAGCGCCCGCGTCCGGGGATC GGGATGTCCCTCCTCCTCTTGCTAGTTTCCTACTATGTTGGAACCTTGGGGACTCA CACTGAGATCAAGAGTGGCAGAGGAAAAGGTCACTTTGCCCTGCCACCATCAACTGGGGC TTCCAGAAAAGACACTCTGGATATTGAATGGCTGCTCACCGATAATGAAGGGAACCAAAAA GTGGTGATCACTTACTCCAGTCGTCATGTCTACAATAACTTGACTGAGGAACAGAAGGGCCG AGTGGCCTTTGCTTCCAATTTCCTGGCAGGAGATGCCTCCTTGCAGATTGAACCTCTGAAGC CCAGTGATGAGGGCCGGTACACCTGTAAGGTTAAGAATTCAGGGCCGCTACGTGTGGAGCCAT GTCATCTTAAAAGTCTTAGTGAGACCATCCAAGCCCAAGTGTGAGTTGGAAGGAGAGCTGAC AGAAGGAAGTGACCTGACTTTGCAGTGTGAGTCATCCTCTGGCACAGAGCCCATTGTGTATT ACTGGCAGCGAATCCGAGAGAAAGAGGGAGAGGATGAACGTCTGCCTCCCAAATCTAGGATT GACTACAACCACCTGGACGAGTTCTGCTGCAGAATCTTACCATGTCCTACTCTGGACTGTA CCAGTGCACAGCAGCAACGAAGCTGGGAAGGAAAGCTGTGTGGTGCGAGTAACTGTACAGT ATGTACAAAGCATCGGCATGGTTGCAGGAGCAGTGACAGGCATAGTGGCTGGAGCCCTGCTG GAGACCTAATGAAATTCGAGAAGATGCTGAAGCTCCAAAAGCCCGTCTTGTGAAACCCAGCT CCTCTTCCTCAGGCTCTCGGAGCTCACGCTCTGGTTCTTCCTCCACTCGCTCCACAGCAAAT ACGGTCTGAATTACAATGGACTTGACTCCCACGCTTTCCTAGGAGTCAGGGTCTTTGGACTC TTCTCGTCATTGGAGCTCAAGTCACCAGCCACACCAGATGAGAGGTCATCTAAGTAGCA GTGAGCATTGCACGGAACAGATTCAGATGAGCATTTTCCTTATACAATACCAAACAAGCAAA AGGATGTAAGCTGATTCATCTGTAAAAAGGCATCTTATTGTGCCTTTAGACCAGAGTAAGGG AAAGCAGGAGTCCAAATCTATTTGTTGACCAGGACCTGTGGTGAGAAGGTTGGGGAAAGGTG AGGTGAATATACCTAAAACTTTTAATGTGGGATATTTTGTATCAGTGCTTTGATTCACAATT TTCAAGAGGAAATGGGATGCTGTTTGTAAATTTTCTATGCATTTCTGCAAACTTATTGGATT ATTAGTTATTCAGACAGTCAAGCAGAACCCACAGCCTTATTACACCTGTCTACACCATGTAC TGAGCTAACCACTTCTAAGAAACTCCAAAAAAGGAAACATGTGTCTTCTATTCTGACTTAAC TTCATTTGTCATAAGGTTTGGATATTAATTTCAAGGGGAGTTGAAATAGTGGGAGATGGAGA AGAGTGAATGAGTTTCTCCCACTCTATACTAATCTCACTATTTGTATTGAGCCCAAAATAAC TATGAAAGGAGACAAAAATTTGTGACAAAGGATTGTGAAGAGCTTTCCATCTTCATGATGTT ATGAGGATTGTTGACAAACATTAGAAATATATAATGGAGCAATTGTGGATTTCCCCTCAAAT CAGATGCCTCTAAGGACTTTCCTGCTAGATATTTCTGGAAGGAGAAAATACAACATGTCATT TATCAACGTCCTTAGAAAGAATTCTTCTAGAGAAAAAGGGATCTAGGAATGCTGAAAGATTA CCCAACATACCATTATAGTCTCTTCTTTCTGAGAAAATGTGAAACCAGAATTGCAAGACTGG TGGTGCCAGGCACCTGTAGGAAAATCCAGCAGGTGGAGGTTGCAGTGAGCCGAGATTATGCC ATTGCACTCCAGCCTGGGTGACAGAGCGGGACTCCGTCTC

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FIGURE 316

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA45419

><subunit 1 of 1, 373 aa, 1 stop

><MW: 41281, pI: 8.33, NX(S/T): 3

MSLLLLLLVSYYVGTLGTHTEIKRVAEEKVTLPCHHQLGLPEKDTLDIEWLLTDNEGNQKV VITYSSRHVYNNLTEEQKGRVAFASNFLAGDASLQIEPLKPSDEGRYTCKVKNSGRYVWSHV ILKVLVRPSKPKCELEGELTEGSDLTLQCESSSGTEPIVYYWQRIREKEGEDERLPPKSRID YNHPGRVLLQNLTMSYSGLYQCTAGNEAGKESCVVRVTVQYVQSIGMVAGAVTGIVAGALLI FLLVWLLIRRKDKERYEEEERPNEIREDAEAPKARLVKPSSSSSGSRSSRSGSSSTRSTANS ASRSORTLSTDAAPOPGLATQAYSLVGPEVRGSEPKKVHHANLTKAETTPSMIPSQSRAFQTV

Signal sequence:

amino acids 1-16

Transmembrane domain:

amino acids 232-251

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FIGURE 317

 ${\tt CCATG}$ GCGCTCCTGCTGCTCCTGTGCGGGGGTAGTGGATTTCGCCAGAAGTTTGAGTATCACTACT CCTGAAGAGATGATTGAAAAAGCCAAAGGGGAAACTGCCTATCTGCCATGCAAATTTACGCTTAGTCCCGAAGA CCAGGGACCGCTGGACATCGAGTGGCTGATATCACCAGCTGATAATCAGAAGGTGGATCAAGTGATTATTTTAT ATTCTGGAGACAAAATTTATGATGACTACTATCCAGATCTGAAAGGCCGAGTACATTTTACGAGTAATGATCTC **AAATCTGGTGATGCATCAATAAATGTAACGAATTTACAACTGTCAGATATTGGCACATATCAGTGCAAAGTGAA** AAAAGCTCCTGGTGTTGCAAATAAGAAGATTCATCTGGTAGTTCTTGTTAAGCCTTCAGGTGCGAGATGTTACG TTGATGGATCTGAAGAAATTGGAAGTGACTTTAAGATAAAATGTGAACCAAAAGAAGGTTCACTTCCATTACAG TATGAGTGGCAAAAATTGTCTGACTCACAGAAAATGCCCACTTCATGGTTAGCAGAAATGACTTCATCTGTTAT ATCTGTAAAAAATGCCTCTTCTGAGTACTCTGGGACATACAGCTGTACAGTCAGAAACAGAGTGGGCTCTGATC AGTGCCTGTTGCGTCTAAACGTTGTCCCTCCTTCAAATAAAGCTGGACTAATTGCAGGAGCCATTATAGGAACT TTGCTTGCTCTAGCGCTCATTGGTCTTATCATCTTTTGCTGTCGTAAAAAGCGCAGAGAAGAAAAATATGAAAA GGAAGTTCATCACGATATCAGGGAAGATGTGCCACCTCCAAAGAGCCGTACGTCCACTGCCAGAAGCTACATCG GCAGTAATCATTCATCCCTGGGGTCCATGTCTCCTTCCAACATGGAAGGATATTCCAAGACTCAGTATAACCAA GTACCAAGTGAAGACTTTGAACGCACTCCTCAGAGTCCGACTCTCCCACCTGCTAAGTTCAAGTACCCTTACAA GACTGATGGAATTACAGTTGTA**TAA**ATATGGACTACTGAAGAATCTGAAGTATTGTATTATTTGACTTTATTTT AGGCCTCTAGTAAAGACTTAAATGTTTTTTAAAAAAAGCACAAGGCACAGAGTTAGAGCAGCTGTAAGAACAC ATCTACTTTATGCAATGGCATTAGACATGTAAGTCAGATGTCATGTCAAAATTAGTACGAGCCAAATTCTTTGT TAAAAAACCCTATGTATAGTGACACTGATAGTTAAAAGATGTTTTATTATATTTTCAATAACTACCACTAACAA $\textbf{ATTTTAACTTTCATATGCATATTCTGATATGTGGTCTTTTAGGAAAAGTATGGTTAATAGTTGATTTTCAA$ AGGAAATTTTAAAATTCTTACGTTCTGTTTAATGTTTTTGCTATTTAGTTAAATACATTGAAGGGAAATACCCG TTCTTTTCCCCTTTTATGCACACAACAGAAACACGCGTTGTCATGCCTCAAACTATTTTTTATTTGCAACTACA TAAAGTAAATTCTCAAAGGTGCTAGAACAAATCGTCCACTTCTACAGTGTTCTCGTATCCAACAGAGTTGATGC ACAATATATAAATACTCAAGTCCAATATTAAAAACTTAGGCACTTGACTAACTTTAATAAAATTTCTCAAACTA TATCAATATCTAAAGTGCATATATTTTTTAAGAAAGATTATTCTCAATAACTTCTATAAAAATAAGTTTGATGG TTTGGCCCATCTAACTTCACTACTATTAGTAAGAACTTTTAACTTTTAATGTGTAGTAAGGTTTATTCTACCTT TTTCTCAACATGACACCAACACAATCAAAAACGAAGTTAGTGAGGTGCTAACATGTGAGGATTAATCCAGTGAT TGATTTGGATAACCAAATGGAACAGGAGGAGGATAGTGATTCTGATGGCCATTCCCTCGATACATTCCTGGCTT TTTTCTGGGCAAAGGGTGCCACATTGGAAGAGGTGGAAATATAAGTTCTGAAATCTGTAGGGAAGAGAACACAT TAAGTTAATTCAAAGGAAAAATCATCATCTATGTTCCAGATTTCTCATTAAAGACAAAGTTACCCACAACACT GAGATCACATCTAAGTGACACTCCTATTGTCAGGTCTAAATACATTAAAAAACCTCATGTGTAATAGGCGTATAA TGTATAACAGGTGACCAATGTTTTCTGAATGCATAAAGAAATGAATAAACTCAAACACAGTACTTCCTAAACAA CTTCAACCAAAAAAGACCAAAACATGGAACGAATGGAAGCTTGTAAGGACATGCTTGTTTTAGTCCAGTGGTTT CCACAGCTGGCTAAGCCAGGAGTCACTTGGAGGCTTTTAAATACAAAACATTGGAGCTGGAGGCCATTATCCTT AGCAAACTAATGCAGAAACAGAAAATCAACTACCGCATGTTCTCACTTATAAGTGGGAGGTAATGATAAGAACT GAAAAGATAACTATTGAGTACTGCCTTCACACCTGGGTGATGAAATAATATGTACAACAAATCCCTGTGACACA **АААААААААААААААААААА**

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FIGURE 318

></usr/seqdb2/sst/DNA/Dnaseqs.full/ss.DNA82361

><subunit 1 of 1, 352 aa, 1 stop

><MW: 38938, pI: 7.86, NX(S/T): 3

MALLLCFVLLCGVVDFARSLSITTPEEMIEKAKGETAYLPCKFTLSPEDQGPLDIEWLISPA DNQKVDQVIILYSGDKIYDDYYPDLKGRVHFTSNDLKSGDASINVTNLQLSDIGTYQCKVKK APGVANKKIHLVVLVKPSGARCYVDGSEEIGSDFKIKCEPKEGSLPLQYEWQKLSDSQKMPT SWLAEMTSSVISVKNASSEYSGTYSCTVRNRVGSDQCLLRLNVVPPSNKAGLIAGAIIGTLL ALALIGLIIFCCRKKRREEKYEKEVHHDIREDVPPPKSRTSTARSYIGSNHSSLGSMSPSNM EGYSKTQYNQVPSEDFERTPQSPTLPPAKFKYPYKTDGITVV

Signal sequence.

amino acids 1-19

Transmembrane domain:

amino acids 236-257

N-glycosylation sites.

amino acids 106-110, 201-205, 298-302

Tyrosine kinase phosphorylation sites.

amino acids 31-39, 78-85, 262-270

N-myristoylation sites.

amino acids 116-122, 208-214, 219-225, 237-243, 241-247, 245-251, 296-302

Myelin P0 protein.

amino acids 96-125

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FIGURE 319

CTCAAGCATCACTTACAGGACCAGAGGGACAAGACATGACTGTGATGAGGAGCTGCTTTCGC CAATTTAACACCAAGAAGAATTGAGGCTGCTTGGGAGGAAGGCCAGGAGGAACACGAGACTG AGAGATGAATTTTCAACAGAGGCTGCAAAGCCTGTGGACTTTAGCCAGACCCTTCTGCCCTC CTTTGCTGGCGACAGCCTCTCAAATGCAGATGGTTGTGCTCCCTTGCCTGGGTTTTACCCTG CTTCTCTGGAGCCAGGTATCAGGGGCCCAGGGCCAAGAATTCCACTTTGGGCCCTGCCAAGT GAAGGGGGTTGTTCCCCAGAAACTGTGGGAAGCCTTCTGGGCTGTGAAAGACACTATGCAAG CTCAGGATAACATCACGAGTGCCCGGCTGCTGCAGCAGGAGGTTCTGCAGAACGTCTCGGAT GCTGAGAGCTGTTACCTTGTCCACACCCTGCTGGAGTTCTACTTGAAAAACTGTTTTCAAAAA CCACCACAATAGAACAGTTGAAGTCAGGACTCTGAAGTCATTCTCTACTCTGGCCAACAACT TTGTTCTCATCGTGTCACAACTGCAACCCAGTCAAGAAAATGAGATGTTTTCCATCAGAGAC AGTGCACACAGGCGGTTTCTGCTATTCCGGAGAGCATTCAAACAGTTGGACGTAGAAGCAGC TCTGACCAAAGCCCTTGGGGAAGTGGACATTCTTCTGACCTGGATGCAGAAATTCTACAAGC TCTGAATGTCTAGACCAGGACCTCCCTCCCCTGGCACTGGTTTGTTCCCTGTGTCATTTCA AACAGTCTCCCTTCCTATGCTGTTCACTGGACACTTCACGCCCTTGGCCATGGGTCCCATTC TTGGCCCAGGATTATTGTCAAAGAAGTCATTCTTTAAGCAGCGCCAGTGACAGTCAGGGAAG AATTAATGTCAGTATTTCAACTGAAGTTCTATTTATTTGTGAGACTGTAAGTTACATGAAGG CAGCAGAATATTGTGCCCCATGCTTCTTTACCCCTCACAATCCTTGCCACAGTGTGGGGCAG GTTAAAAAACAGAGGGATGCTTGGATGTAAAACTGAACTTCAGAGCATGAAAATCACACT TAAACGATAAAATGTGGATTAAAGTGCCCAGCACAAAGCAGATCCTCAATAAACATTTCATT TATCCTAGTCATTCTTCCCTAATCTTCCACTTGAGTGTCAAGCTGACCTTGCTGATGGTGAC ATTGCACCTGGATGTACTATCCAATCTGTGATGACATTCCCTGCTAATAAAAGACAACATAA СТССАААААААААААААААААААААА

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FIGURE 320

></usr/seqdb2/sst/DNA/Dnaseqs.full/ss.DNA88002

><subunit 1 of 1, 206 aa, 1 stop

><MW: 23799, pI: 9.12, NX(S/T): 3

MNFQQRLQSLWTLARPFCPPLLATASQMQMVVLPCLGFTLLLWSQVSGAQGQEFHFGPCQVK GVVPQKLWEAFWAVKDTMQAQDNITSARLLQQEVLQNVSDAESCYLVHTLLEFYLKTVFKNH HNRTVEVRTLKSFSTLANNFVLIVSQLQPSQENEMFSIRDSAHRRFLLFRRAFKQLDVEAAL TKALGEVDILLTWMQKFYKL

Signal sequence:

amino acids 1-42

N-glycosylation sites.

amino acids 85-89, 99-103, 126-130

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FIGURE 321

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FIGURE 322

></usr/seqdb2/sst/DNA/Dnaseqs.full/ss.DNA92282

><subunit 1 of 1, 177 aa, 1 stop

><MW: 20452, pI: 8.00, NX(S/T): 2

MKLQCVSLWLLGTILILCSVDNHGLRRCLISTDMHHIEESFQEIKRAIQAKDTFPNVTILST LETLQIIKPLDVCCVTKNLLAFYVDRVFKDHQEPNPKILRKISSIANSFLYMQKTLRQCQEQ RQCHCRQEATNATRVIHDNYDQLEVHAAAIKSLGELDVFLAWINKNHEVMFSA

Signal sequence:

amino acids 1-18

N-glycosylation sites.

amino acids 56-60, 135-139

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 102-106

N-myristoylation site.

amino acids 24-30

Actinin-type actin-binding domain signature 1.

amino acids 159-169

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FIGURE 323

CCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACTTGGCTTCGTTAG AACGCGGCTACAATTAATACATAACCTTATGTATCATACACATACGATTTAGGTGACACTAT AGAATAACATCCACTTTGCCTTTCTCCACAGGTGTCCACTCCCAGGTCCAACTGCACCTC GGTTCTATCGATAATCTCAGCACCAGCCACTCAGAGCAGGGCACGATGTTGGGGGGCCCGCCT CAGGCTCTGGGTCTGTGCCTTGTGCAGCGTCTGCAGCATGAGCGTCCTCAGAGCCTATCCCA ATGCCTCCCACTGCTCGGCTCCAGCTGGGGTGGCCTGATCCACCTGTACACAGCCACAGCC AGGAACAGCTACCACCTGCAGATCCACAAGAATGGCCATGTGGATGGCGCACCCCATCAGAC CATCTACAGTGCCCTGATGATCAGATCAGAGGATGCTGGCTTTGTGGTGATTACAGGTGTGA TGAGCAGAAGATACCTCTGCATGGATTTCAGAGGCAACATTTTTGGATCACACTATTTCGAC CCGGAGAACTGCAGGTTCCAACACCAGACGCTGGAAAACGGGTACGACGTCTACCACTCTCC TCAGTATCACTTCCTGGTCAGTCTGGGCCGGGCGAAGAGAGCCTTCCTGCCAGGCATGAACC CACCCCGTACTCCCAGTTCCTGTCCCGGAGGAACGAGATCCCCCTAATTCACTTCAACACC CCCATACCACGGGGGCACACCCGGAGCGCCGAGGACGACTCGGAGCGGGACCCCCTGAACGT GCTGAAGCCCCGGGCCCGGATGACCCCGGCCCCGGCCTCCTGTTCACAGGAGCTCCCGAGCG CCGAGGACAACAGCCCGATGGCCAGTGACCCATTAGGGGTGGTCAGGGGCGGTCGAGTGAAC ACGCACGCTGGGGGAACGGCCCGGAAGGCTGCCGCCCCTTCGCCAAGTTCATC**TAG**GGTCG **CTGG**

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FIGURE 324

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA142238</pre>

><subunit 1 of 1, 251 aa, 1 stop

><MW: 27954, pI: 9.22, NX(S/T): 1

MLGARLRLWVCALCSVCSMSVLRAYPNASPLLGSSWGGLIHLYTATARNSYHLQIHKNGHVD GAPHQTIYSALMIRSEDAGFVVITGVMSRRYLCMDFRGNIFGSHYFDPENCRFQHQTLENGY DVYHSPQYHFLVSLGRAKRAFLPGMNPPPYSQFLSRRNEIPLIHFNTPIPRRHTRSAEDDSE RDPLNVLKPRARMTPAPASCSQELPSAEDNSPMASDPLGVVRGGRVNTHAGGTGPEGCRPFA KFI

Important features of the protein:

Signal peptide:

amino acids 1-24

cAMP- and cGMP-dependent protein kinase phosphorylation site.
amino acids 175-179

N-myristoylation site.

amino acids 33-39, 100-106, 225-231, 229-235

HBGF/FGF family proteins

amino acids 73-124

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FIGURE 325

GGAAAAGGTACCCGCGAGAGACAGCCAGCAGTTCTGTGGAGCAGCGGTGGCCGGCTAGG<u>ATG</u> GAGCTCTGCAGGCCCCAGCACCCGCAGAGCAGACACTGCGATGACAACGGACGACACAGAAG TGCCCGCTATGACTCTAGCACCGGGCCACGCCGCTCTGGAAACTCAAACGCTGAGCGCTGAG ACCTCTTCTAGGGCCTCAACCCCAGCCGGCCCCATTCCAGAAGCAGAGACCAGGGGAGCCAA GAGAATTTCCCCTGCAAGAGAGACCAGGAGTTTCACAAAAACATCTCCCAACTTCATGGTGC TGATCGCCACCTCCGTGGAGACATCAGCCGCCAGTGGCAGCCCCGAGGGAGCTGGAATGACC ACAGTTCAGACCATCACAGGCAGTGATCCCGAGGAAGCCATCTTTGACACCCTTTGCACCGA TGACAGCTCTGAAGAGGCAAAGACACTCACAATGGACATATTGACATTGGCTCACACCTCCA CAGAAGCTAAGGGCCTGTCCTCAGAGAGCAGTGCCTCTTCCGACGGCCCCCATCCAGTCATC ACCCCGTCACGGCCTCAGAGAGCAGCGCCTCTTCCGACGCCCCCATCCAGTCATCACCCC GTCACGGGCCTCAGAGAGCAGCGCCTCTTCCGACGGCCCCCATCCAGTCATCACCCCGTCAT GGTCCCCGGGATCTGATGTCACTCTCCTCGCTGAAGCCCTGGTGACTGTCACAAACATCGAG GTTATTAATTGCAGCATCACAGAAATAGAAACAACAACTTCCAGCATCCCTGGGGCCTCAGA ${\tt CATAGATCTCATCCCCACGGAAGGGGTGAAGGCCTCGTCCACCTCCGATCCACCAGCTCTGC}$ CTGACTCCACTGAAGCAAAACCACACATCACTGAGGTCACAGCCTCTGCCGAGACCCTGTCC ACAGCCGGCACCACAGAGTCAGCTGCACCTCATGCCACGGTTGGGACCCCACTCCCCACTAA CAGCGCCACAGAAAGAGAAGTGACAGCACCCGGGGCCACGACCCTCAGTGGAGCTCTGGTCA CAGTTAGCAGGAATCCCCTGGAAGAAACCTCAGCCCTCTCTGTTGAGACACCAAGTTACGTC AAAGTCTCAGGAGCAGCTCCGGTCTCCATAGAGGCTGGGTCAGCAGTGGGCAAAACAACTTC CTTTGCTGGGAGCTCTGCTTCCTCCTACAGCCCCTCGGAAGCCGCCCTCAAGAACTTCACCC CTTCAGAGACACCGACCATGGACATCGCAACCAAGGGGCCCTTCCCCACCAGCAGGGACCCT CTTCCTTCTGTCCCTCCGACTACAACCAACAGCAGCCGAGGGACGAACAGCACCTTAGCCAA GATCACAACCTCAGCGAAGACCACGATGAAGCCCCAACAGCCACGCCCACGACTGCCCGGAC GAGGCCGACCACAGACGTGAGTGCAGGTGAAAATGGAGGTTTCCTCCTCCTGCGGCTGAGTG TGGCTTCCCCGGAAGACCTCACTGACCCCAGAGTGGCAGAAAGGCTGATGCAGCAGCTCCAC CGGGAACTCCACGCCCACGCCCTCACTTCCAGGTCTCCTTACTGCGTGTCAGGAGAGGCTA ACGGACATCAGCTGCAGCCAGGCATGTCCCGTATGCCAAAAGAGGGTGCTGCCCCTAGCCTG GGCCCCACCGACAGACTGCAGCTGCGTTACTGTGCTGAGAGGTTACCCAGAAGGTTCCCATG AAGGGCAGCATGTCCAAGCCCCTAACCCCAGATGTGGCAACAGGACCCTCGCTCACATCCAC CGGAGTGTATGTATGGGGAGGGGCTTCACCTGTTCCCAGAGGTGTCCTTGGACTCACCTTGG CACATGTTCTGTGTTTCAGTAAAGAGAGACCTGATCACCCATCTGTGTGCTTCCATCCTGCA TTAAAATTCACTCAGTGTGGCCCAAAAAAAA

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FIGURE 326

MGCLWGLALPLFFFCWEVGVSGSSAGPSTRRADTAMTTDDTEVPAMTLAPGHAALETQTLSA
ETSSRASTPAGPIPEAETRGAKRISPARETRSFTKTSPNFMVLIATSVETSAASGSPEGAGM
TTVQTITGSDPEEAIFDTLCTDDSSEEAKTLTMDILTLAHTSTEAKGLSSESSASSDGPHPV
ITPSRASESSASSDGPHPVITPSRASESSASSDGPHPVITPSWSPGSDVTLLAEALVTVTNI
EVINCSITEIETTTSSIPGASDIDLIPTEGVKASSTSDPPALPDSTEAKPHITEVTASAETL
STAGTTESAAPHATVGTPLPTNSATEREVTAPGATTLSGALVTVSRNPLEETSALSVETPSY
VKVSGAAPVSIEAGSAVGKTTSFAGSSASSYSPSEAALKNFTPSETPTMDIATKGPFPTSRD
PLPSVPPTTTNSSRGTNSTLAKITTSAKTTMKPQQPRPRLPGRGRPQT

N-glycosylation sites:

amino acids 252-256, 445-449, 451-455

cAMP-and cGMP-dependent protein kinase phosphorylation site. amino acids 84-90

Casein kinase II phosphorylation sites.

amino acids 37-41, 108-112, 131-135, 133-137, 148-152, 165-169, 246-250, 254-258, 256-260, 269-273, 283-287, 333-337, 335-339, 404-408, 414-418, 431-435

N-myristoylation sites.

amino acids 2-8, 19-25, 117-123, 121-127, 232-238, 278-284, 314-320, 349-355, 386-392, 397-403, 449-455

ATP/GTP-binding site motif A (P-loop).

amino acids 385-393

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FIGURE 327

GCGGAGCATCCGCTGCGGTCCTCGCCGAGACCCCCGCGCGGATTCGCCGGTCCTTCCCGCGG GCGCGACAGAGCTGTCCTCGCACCTGGATGGCAGCAGGGGCGCCGGGGTCCTCTCGACGCCA CCTTGACCTTTGAAGACCAAAACTAAACTGAAATTTAAA**ATG**TTCTTCGGGGGGAGAAGGGAG CTTGACTTACACTTTGGTAATAATTTGCTTCCTGACACTAAGGCTGTCTGCTAGTCAGAATT GCCTCAAAAAGAGTCTAGAAGATGTTGTCATTGACATCCAGTCATCTCTTTCTAAGGGAATC AGAGGCAATGAGCCCGTATATACTTCAACTCAAGAAGACTGCATTAATTCTTGCTGTTCAAC AAAAAACATATCAGGGGACAAAGCATGTAACTTGATGATCTTCGACACTCGAAAAACAGCTA GACAACCCAACTGCTACCTATTTTTCTGTCCCAACGAGGAAGCCTGTCCATTGAAACCAGCA AAAGGACTTATGAGTTACAGGATAATTACAGATTTTCCATCTTTGACCAGAAATTTGCCAAG CCAAGAGTTACCCCAGGAAGATTCTCTCTTACATGGCCAATTTTCACAAGCAGTCACTCCCC TAGCCCATCATCACACAGATTATTCAAAGCCCACCGATATCTCATGGAGAGACACACTTTCT GCTCCTTGCTTATAAGGAAAAAGGCCATTCTCAGAGTTCACAATTTTCCTCTGATCAAGAAA TAGCTCATCTGCTGCCTGAAAATGTGAGTGCGCTCCCAGCTACGGTGGCAGTTGCTTCTCCA CATACCACCTCGGCTACTCCAAAGCCCGCCACCCTTCTACCCACCAATGCTTCAGTGACACC TTCTGGGACTTCCCAGCCACAGCTGGCCACCACAGCTCCACCTGTAACCACTGTCACTTCTC AGCCTCCCACGACCCTCATTCTACAGTTTTTACACGGGCTGCGGCTACACTCCAAGCAATG GCTACAACAGCAGTTCTGACTACCACCTTTCAGGCACCTACGGACTCGAAAGGCAGCTTAGA AACCATACCGTTTACAGAAATCTCCAACTTAACTTTGAACACAGGGAATGTGTATAACCCTA CTGCACTTTCTATGTCAAATGTGGAGTCTTCCACTATGAATAAAACTGCTTCCTGGGAAGGT AGGGAGGCCAGTCCAGGCAGTTCCTCCCAGGGCAGTGTTCCAGAAAATCAGTACGGCCTTCC ATTTGAAAAATGGCTTCTTATCGGGTCCCTGCTCTTTGGTGTCCTGTTCCTGGTGATAGGCC TCGTCCTCCTGGGTAGAATCCTTTCGGAATCACTCCGCAGGAAACGTTACTCAAGACTGGAT TATTTGATCAATGGGATCTATGTGGACATCTAAGGATGGAACTCGGTGTCTCTTAATTCATT TAGTAACCAGAAGCCCAAATGCAATGAGTTTCTGCTGACTTGCTAGTCTTAGCAGGAGGTTG GCTCTGTTGCCCAGGCTGGAGTGCAGTAGCACGATCTCGGCTCTCACCGCAACCTCCGTCTC CTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCTAAGTATCTGGGATTACAGGCATGTGCCA CCACACCTGGGTGATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGTCAGGCTG GTCTCAAACTCCTGACCTAGTGATCCACCCTCCTCGGCCTCCCAAAGTGCTGGGATTACAGG CATGAGCCACCACAGCTGGCCCCCTTCTGTTTTATGTTTTGGTTTTTGAGAAGGAATGAAGTG GGAACCAAATTAGGTAATTTTGGGTAATCTGTCTCTAAAATATTAGCTAAAAACAAAGCTCT ATGTAAAGTAATAAGTATAATTGCCATATAAATTTCAAAATTCAACTGGCTTTTATGCAAA GAAACAGGTTAGGACATCTAGGTTCCAATTCATTCACATTCTTGGTTCCAGATAAAATCAAC TGTTTATATCAATTCTAATGGATTTGCTTTTCTTTTTATATGGATTCCTTTAAAACTTATT CCAGATGTAGTTCCTTCCAATTAAATATTTGAATAAATCTTTTGTTACTCAA

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FIGURE 328

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA45410

><subunit 1 of 1, 431 aa, 1 stop

><MW: 46810, pI: 6.45, NX(S/T): 6

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Signal sequence.

amino acids 1-25

Transmembrane domain.

amino acids 384-405

N-glycosylation sites.

amino acids 72-76, 222-226, 251-255, 327-331, 352-356

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 415-419

Tyrosine kinase phosphorylation site.

amino acids 50-57

N-myristoylation sites.

amino acids 4-10, 48-54, 315-321

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FIGURE 329

CTCCCACGGTGTCCAGCGCCCAGA**ATG**CGGCTTCTGGTCCTGCTATGGGGTTGCCTGCTGCT CCCAGGTTATGAAGCCCTGGAGGGCCCAGAGGAAATCAGCGGGTTCGAAGGGGACACTGTGT CCCTGCAGTGCACCTACAGGGAAGAGCTGAGGGACCACCGGAAGTACTGGTGCAGGAAGGGT GGGATCCTCTCTCTCGCTGCTCTGGCACCATCTATGCAGAAGAAGAAGGCCAGGAGACAAT GAAGGCAGGGTGTCCATCCGTGACAGCCGCCAGGAGCTCTCGCTCATTGTGACCCTGTGGA ACCTCACCCTGCAAGACGCTGGGGAGTACTGGTGTGGGGTCGAAAAACGGGGCCCCGATGAG TCTTTACTGATCTCTGTTCGTCTTTCCAGGACCCTGCTGTCCTCCCCTCCCCTTCTCCCAC CTTCCAGCCTCTGGCTACAACACGCCTGCAGCCCAAGGCAAAAGCTCAGCAAACCCAGCCCC CAGGATTGACTTCTCCTGGGCTCTACCCGGCAGCCACCACAGCCAAGCAGGGGAAGACAGGG GCTGAGGCCCCTCCATTGCCAGGGACTTCCCAGTACGGCACGAAAGGACTTCTCAGTACAC AGGAACCTCTCCTCACCCAGCGACCTCTCCTCCTGCAGGGAGCTCCCGCCCCCCCATGCAGC TGGACTCCACCTCAGCAGAGGACACCAGTCCAGCTCTCAGCAGTGGCAGCTCTAAGCCCAGG GTGTCCATCCCGATGGTCCGCATACTGGCCCCAGTCCTGGTGCTGAGCCTTCTGTCAGC CGCAGGCCTGATCGCCTTCTGCAGCCACCTGCTCCTGTGGAGAAAGGAAGCTCAACAGGCCA CGGAGACACAGAGGAACGAGAAGTTCTGGCTCTCACGCTTGACTGCGGAGGAAAAGGAAGCC CCTTCCCAGGCCCCTGAGGGGGACGTGATCTCGATGCCTCCCCTCCACACATCTGAGGAGGA GCTGGGCTTCTCGAAGTTTGTCTCAGCG**TAG**GGCAGGAGGCCCTCCTGGCCAGGCCAGCAGT GAAGCAGTATGGCTGGCTGGATCAGCACCGATTCCCGAAAGCTTTCCACCTCAGCCTCAGAG TCCAGCTGCCCGGACTCCAGGGCTCTCCCCACCTCCCAGGCTCTCCTCTTGCATGTTCCA GCCTGACCTAGAAGCGTTTGTCAGCCCTGGAGCCCAGAGCGGTGGCCTTGCTCTTCCGGCTG GAGACTGGGACATCCCTGATAGGTTCACATCCCTGGGCAGAGTACCAGGCTGCTGACCCTCA GCAGGCCAGACAAGGCTCAGTGGATCTGGTCTGAGTTTCAATCTGCCAGGAACTCCTGGGC TGGCGTCCTCAGACTTAGTCCCACGGTCTCCTGCATCAGCTGGTGATGAAGAGGAGCATGCT GGGGTGAGACTGGGATTCTGGCTTCTCTTTGAACCACCTGCATCCAGCCCTTCAGGAAGCCT GTGAAAAACGTGATTCCTGGCCCCACCAAGACCCACCAAAACCATCTCTGGGCTTGGTGCAG GACTCTGAATTCTAACAATGCCCAGTGACTGTCGCACTTGAGTTTGAGGGCCAGTGGGCCTG ATGAACGCTCACACCCCTTCAGCTTAGAGTCTGCATTTGGGCTGTGACGTCTCCACCTGCCC CAATAGATCTGCTCTGTCTGCGACACCAGATCCACGTGGGGACTCCCCTGAGGCCTGCTAAG TCCAGGCCTTGGTCAGGTCAGGTGCACATTGCAGGATAAGCCCAGGACCGGCACAGAAGTGG TTGCCTTTNCCATTTGCCCTCCCTGGNCCATGCCTTCTTGCCTTTGGAAAAAATGATGAAGA AAACCTTGGCTCCTTGTCTGGAAAGGGTTACTTGCCTATGGGTTCTGGTGGCTAGAGA GAAAAGTAGAAAACCAGAGTGCACGTAGGTGTCTAACACAGAGGAGAGTAGGAACAGGGCGG ATACCTGAAGGTGACTCCGAGTCCAGCCCCCTGGAGAAGGGGTCGGGGGTGGTGATAAGTA GCACAACTACTATTTTTTTTCTTTTTCCATTATTATTGTTTTTTAAGACAGAATCTCGTGCT GCTGCCCAGGCTGGAGTGCAGTGGCACGATCTGCAAACTCCGCCTCCTGGGTTCAAGTGATT TTTGTACTTTTAGTAGAGATGGGGTTTCACCATGTTGGCCAGGCTGGTCTTGAACTCCTGAC CTCAAATGAGCCTCCTGCTTCAGTCTCCCAAATTGCCGGGATTACAGGCATGAGCCACTGTG TCTGGCCCTATTTCCTTTAAAAAGTGAAATTAAGAGTTGTTCAGTATGCAAAACTTGGAAAG ATGGAGGAGAAAAGGAAAGGAAGAAAAAATGTCACCCATAGTCTCACCAGAGACTATCAT TATTTCGTTTTGTTGTACTTCCTTCCACTCTTTTCTTCTCACATAATTTGCCGGTGTTCTT TTTACAGAGCAATTATCTTGTATATACAACTTTGTATCCTGCCTTTTCCACCTTATCGTTCC GCTGCATAAAAAAAAAAAAA

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FIGURE 330

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA44196</pre>

<subunit 1 of 1, 332 aa, 1 stop

<MW: 36143, pI: 5.89, NX(S/T): 1

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Important features:

Signal peptide:

amino acids 1-17

Transmembrane domain:

amino acids 248-269

N-glycosylation site.

amino acids 96-99

Fibrinogen beta and gamma chains C-terminal domain.

amino acids 104-113

Ig like V-type domain:

amino acids 13-128

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 00/08439

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/12 C07K14/47 C07K14/705 C12N15/62 C07K16/18 A61K38/17 G01N33/53 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N CO7K GO1N A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) STRAND C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ° Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. WO 98 39448 A (HUMAN GENOME SCIENCES INC) X 1-28 11 September 1998 (1998-09-11) see passages relating to gene 174 (clone H2MBF44) and the claims. WO 98 42741 A (GENETICS INST) X 1-28 1 October 1998 (1998-10-01) see passages relating to clone ck181_7 and the claims. EP 0 834 563 A (SMITHKLINE BEECHAM CORP.) A 8 April 1998 (1998-04-08) the whole document WO 97 07198 A (GENETICS INST) A 27 February 1997 (1997-02-27) the whole document -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or other means ments, such combination being obvious to a person skilled in the art. "P" document published prior to the International filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 1 3, 11, 00 16 August 2000 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Smalt, R Fax: (+31-70) 340-3016

nternational	Application No
PCT/US	00/08439

Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
YOKOYAMA-KOBAYASHI M ET AL: "A signal sequence detection system using secreted protease activity as an indicator" GENE,NL,ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 163, no. 2, 3 October 1995 (1995-10-03), pages 193-196, XP004041983 ISSN: 0378-1119 the whole document	
KLEIN R D ET AL: "Selection for genes encoding secreted proteins and receptors" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, US, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, no. 93, 1 July 1996 (1996-07-01), pages 7108-7113, XP002077277 ISSN: 0027-8424 the whole document	
WO 99 63088 A (BAKER KEVIN; CHEN JIAN (US); GENENTECH INC (US); YUAN JEAN (US); G) 9 December 1999 (1999-12-09) see passages relating to PRO281 and the claims. L: priority.	1-28
WO 99 46375 A (SCHMITT ARMIN ;SPECHT THOMAS (DE); DAHL EDGAR (DE); HINZMANN BERND) 16 September 1999 (1999-09-16) see whole document, particularly passages relating to seq.ID'2 219 and 251	1-13, 17-28
WO 99 53040 A (SCHMITT ARMIN ;SPECHT THOMAS (DE); DAHL EDGAR (DE); HINZMANN BERND) 21 October 1999 (1999-10-21) page 1 -page 8 see claims. page 128	1-13, 17-22, 24-28
WO 00 08145 A (NOVARTIS ERFINDUNGEN VERWALTUN; NOVARTIS AG (CH); HOLNESS CLAIRE L) 17 February 2000 (2000-02-17) the whole document	1-13, 21-28
WO 99 63083 A (TSURITANI KATSUKI ;ARASE SEIJI (JP); IKEDA AKIKO (JP); TAISHO PHAR) 9 December 1999 (1999-12-09) abstract see sequences.	1-13,21, 22,25-28
	sequence detection system using secreted protease activity as an indicator* GENE,NL,ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 163, no. 2, 3 October 1995 (1995-10-03), pages 193-196, XP004041983 1SSN: 0378-1119 the whole document KLEIN R D ET AL: "Selection for genes encoding secreted proteins and receptors" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, no. 93, 1 July 1996 (1996-07-01), pages 7108-7113, XP002077277 1SSN: 0027-8424 the whole document WO 99 63088 A (BAKER KEVIN ; CHEN JIAN (US); GENENTECH INC (US); YUAN JEAN (US); G DECEMBER 1999 (1999-12-09) see passages relating to PRO281 and the claims. L: priority. WO 99 46375 A (SCHMITT ARMIN ; SPECHT THOMAS (DE); DAHL EDGAR (DE); HINZMANN BERND) 16 September 1999 (1999-09-16) see whole document, particularly passages relating to seq.ID'2 219 and 251 WO 99 53040 A (SCHMITT ARMIN ; SPECHT THOMAS (DE); DAHL EDGAR (DE); HINZMANN BERND) 21 October 1999 (1999-10-21) page 1 -page 8 see claims. page 128 WO 00 08145 A (NOVARTIS ERFINDUNGEN VERWALTUN; NOVARTIS AG (CH); HOLNESS CLAIRE L) 17 February 2000 (2000-02-17) the whole document WO 99 63083 A (TSURITANI KATSUKI ; ARASE SEIJI (JP); IKEDA AKIKO (JP); TAISHO PHAR) 9 December 1999 (1999-12-09) abstract

INTERNATIONAL SEARCH REPORT

International application No. PCT/US 00/08439

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple Inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Claims 1-28, All partially.
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: claims 1-28, all partially

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PRO281 (seq.ID.2), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to PRO281, chimeric protein comprising a portion corresponding to PRO281, antibody against siad protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto.

Subject matter as defined for invention 1 above, but limited to the respective amino acid sequences and cerresponding nucleic acid sequences referred to as:

```
2. PR0276 (seq.ID's 5/6),
3. PR0189 (Seq.ID's 7/8),
4. PR0190 (Seq.ID's 13/14),
5. PR0341 (Seq.ID's 19/20),
6. PR0180 (Seq.ID's 22/23),
7. PR0190 (Seq.ID's 27/28),
9. PR0203 (Seq.ID's 27/28),
9. PR0203 (Seq.ID's 29/30),
10. PR0290 (Seq.ID's 32/33),
11. PR0874 (Seq.ID's 35/36),
12. PR0710 (Seq.ID's 40/41),
13. PR01151 (Seq.ID's 40/41),
14. PR01281 (Seq.ID's 56/57),
16. PR01310 (Seq.ID's 56/57),
16. PR01310 (Seq.ID's 66/67),
17. PR0698 (Seq.ID's 66/67),
18. PR0732 (Seq.ID's 66/67),
19. PR01120 (Seq.ID's 83/84),
20. PR0537 (Seq.ID's 98/99),
21. PR0536 (Seq.ID's 98/99),
22. PR0535 (Seq.ID's 102/103),
24. PR0872 (Seq.ID's 112/113),
25. PR01063 (Seq.ID's 114/115),
26. PR0619 (Seq.ID's 134/135),
27. PR01188 (Seq.ID's 134/135),
29. PR0783 (Seq.ID's 137/138),
30. PR0820 (Seq.ID's 145/146),
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PCT/ISA/ 210
FURTHER INFORMATION CONTINUED FROM
                 31. PRO1080 (Seq.ID's 147/148), 32. PRO1079 (Seq.ID's 150/151),
                 33. PR0793 (Seq.ID's 152/153),

34. PR01016 (Seq.ID's 155/156),

35. PR01013 (Seq.ID's 157/158),

36. PR0937 (Seq.ID's 159/160),
                 37. PRO842 (Seq.ID's 164/165),
38. PRO839 (Seq.ID's 166/167),
                 39. PR01180 (Seq.ID's 168/169),
                 40. PR01134 (Seq.ID's 170/171),
                 41. PRO830 (Seq.ID's 174/175)
                 42. PRO1115 (Seq.ID's 176/177),
43. PRO1277 (Seq.ID's 178/179),
44. PRO1135 (Seq.ID's 180/181),
                 45. PRO1133 (Seq.ID's 188/189),
45. PRO828 (Seq.ID's 188/189),
46. PRO1009 (Seq.ID's 193/194),
47. PRO1007 (Seq.ID's 196/197),
48. PRO1056 (Seq.ID's 198/199),
                 49. PRO826 (Seq.ID's 200/201), 50. PRO819 (Seq.ID's 202/203),
                 51. PR01006 (Seq.ID's 204/205),
                 52. PR01112 (Seq.ID's 206/207),
                 53. PR01074 (Seq.ID's 208/209),
                 54. PR01005 (Seq.ID's 210/211),
                 55. PR01073 (Seq.ID's 212/213),
                 56. PR01152 (Seq.ID's 215/216),
                 57. PRO1136 (Seq.ID's 218/219),
                 58. PRO813 (Seq.ID's 220/221),
                 59. PR0809 (Seq.ID's 222/223),
                 60. PR0791 (Seq.ID's 224/225).
                 61. PR01004 (Seq.ID's 226/227),
                 62. PR01111
                                  (Seq.ID's 228/229),
                 63. PR01344
                                  (Seq.ID's 230/231),
                 64. PR01109
                                  (Seq.ID's 235/236),
                                  (Seq.ID's 240/241),
                 65. PR01383
                 66. PR01003
                                  (Seq.ID's 245/246),
                 67. PR01108
                                  (Seq.ID's 247/248).
                 68. PR01137
                                  (Seq ID's 249/250),
                 69. PR01138 (Seq.ID's 252/253), 70. PR01054 (Seq.ID's 255/256),
                 71. PR0994 (Seq.ID's 257/258),
        3. Claim : 1
                 72. PR0812 (Seq.ID's 259/260)
                 73. PR01069 (Seq.ID's 261/262),
                                  (Seq.ID's 263/264),
                 74. PR01129
                 75. PR01068
                                  (Seq.ID's 265/266),
                                  (Seq.ID's 267/268),
                 76. PR01066
                 77. PR01184
                                  (Seq.ID's 269/270),
                 78. PR01360
                                  (Seq.ID's 271/272),
                 79. PR01029
                                  (Seq.1D's 273/274),
                 80. PR01139
                                  (Seq.ID's 275/276),
                 81. PR01309 (Seq.ID's 277/278),
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PCT/ISAV 210
FURTHER INFORMATION CONTINUED FROM
               82. PR01028 (Seq.ID's 280/281),
               83. PR01027 (Seq.ID's 282/283),
                              (Seq.ID's 284/285),
               84. PR01107
               85. PR01140 (Seq.ID's 286/287),
86. PR01106 (Seq.ID's 288/289),
87. PR01291 (Seq.ID's 290/291),
88. PR01105 (Seq.ID's 292/293),
               89. PR0511 (Seq.ID's 294/295),
               90. PR01104 (Seq.ID's 296/297),
91. PR01100 (Seq.ID's 298/299),
               92. PRO836 (Seq.ID's 300/301),
               93. PRO1141 (Seq.ID's 302/303),
               94. PRO1132 (Seq.ID's 308/309),
95. PRO1346 (Seq.ID's 313/314),
                              (Seq.ID's 318/319),
(Seq.ID's 325/326),
               96. PR01131
               97. PR01281
                              (Seq.ID's 333/334),
               98. PR01064
                              (Seq.ID's 339/340)
               99. PR01379
                              (Seq.ID's 344/345),
               100. PR0844
               101. PRO848 (Seq.ID's 346/347)
102. PRO1097 (Seq.ID's 348/349
                              (Seq.ID's 348/349)
(Seq.ID's 350/351)
               103. PR01153
               104. PR01154
                               (Seq.ID's 352/353)
                              (Seq.ID's 356/357)
               105. PR01182
               106. PRO1155
                               (Seq.ID's 358/359)
               107. PRO1156 (Seq.ID's 360/361)
               108. PRO1098 (Seq.ID's 362/363)
                              (Seq.ID's 364/365)
               109. PR01127
               110. PRO1126 (Seq.ID's 366/367)
                              (Seq.ID's 368/369)
               111. PR01125
               112. PRO1186 (Seq.ID's 370/371)
               113. PRO1198 (Seq.ID's 372/373)
               114. PRO1158 (Seq.ID's 374/375)
               115. PRO1159 (Seq.ID's 376/377)
               116. PRO1124 (Seq.ID's 378/379)
               117. PR01287
                               (Seq.ID's 380/381)
                              (Seq.ID's 386/387)
               118. PR01312
               119. PRO1192 (Seq.ID's 388/389)
               120. PR01160
                               (Seq.ID's 393/394)
                               (Seq.ID's 398/399)
               121. PR01187
               122. PR01185
                               (Seq.ID's 400/401)
               123. PR01345
                                (Seq.ID's 402/403)
                                Seq.ID's 407/408
               124. PR01245
               125. PR01358
                              (Seq.ID's 409/410)
               126. PR01195
                              (Seq.ID's 411/412)
               127. PR01270
                               (Seq.ID's 413/414)
                               (Seq.ID's 415/416)
               128. PR01271
               129. PR01375
                               (Seq.ID's 417/418)
               130. PR01385
                              (Seq.ID's 419/420),
               131. PR01384
                               (Seq.ID's 423/424),
               132. PR09828 (Seq.ID's 510/511).
               For the sake of conciseness, the first subject matter is
               explicitly defined, the other subject matters are defined by
               analogy thereto.
```

4. Claims: Invention 133: claims 1-36,69-74,99-102, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR0943 (seq.ID.118), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to PR0943, chimeric protein comprising a portion corresponding to PR0943, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR0183, PR0184 or PR0185 through interaction with PR0943 and vice versa, method of linking a bioactive molecule to a cell expressing PR0943 using PR0183, PR0184 or PR0185 as binding ligands and vice versa, and method of modulating the activity of PR0943 by binding with PR0183, PR0184 or PR0185, and vice versa.

5. Claims: Inventions 134-136: claims 1-36,69-74,99-102, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PRO183 (seq.ID.495), PR0184 (seq.ID.497) or PR0185 (seq.ID.499), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to said protien, chimeric protein comprising a portion corresponding to said protein, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PRO183, PRO184 or PR0185 through interaction with PR0943 and vice versa. method of linking a bioactive molecule to a cell expressing PRO943 using PRO183, PRO184 or PRO185 as binding ligands and vice versa, and method of modulating the activity of PR0943 by binding with PRO183, PRO184 or PRO185, and vice versa, whereby invention 134 is limited to PRO183, invention 135 is limited to PRO184, and invention 136 is limited to PRO185.

6. Claims: Invention 137: claims 1-28,37-44,75-80,103-106, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR0331 (seq.ID.501), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to PR0331, chimeric protein comprising a portion corresponding to PR0331, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR01133 through interaction with PR0331 and vice versa, method of linking a bioactive molecule to a cell expressing PR0331 using PR01133 as binding ligands and vice versa, and method of modulating the activity of PR0331 by binding with PR01133, and vice versa.

7. Claims: Invention 138: claims 1-28,37-44,75-80,103-106, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR01133 (seq.ID.129), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to said protien, chimeric protein comprising a portion corresponding to said protein, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR01133 through interaction with PR0331 and vice versa, method of linking a bioactive molecule to a cell expressing PR0331 using PR01133 as binding ligands and vice versa, and method of modulating the activity of PR0331 by binding with PR01133, and vice versa.

8. Claims: Invention 139: claims 1-28,45-52,81-86,107-110, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR01387 (seq.ID.422), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to PR01387, chimeric protein comprising a portion corresponding to PR01387, antibody against said protein, the isolated extracellular domain of said protein or a protein with at

least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PRO363 or PRO5723 through interaction with PRO1387 and vice versa, method of linking a bioactive molecule to a cell expressing PRO1387 using PRO363 or PRO5723 as binding ligands and vice versa, and method of modulating the activity of PRO1387 by binding with PRO363 or PRO5723, and vice versa.

9. Claims: Invention 140 and 141: claims 1-28,45-52,81-86, 107-110, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR0363 (seq.ID.503) or PR05723 (seq.ID.505), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to said protein, chimeric protein comprising a portion corresponding to said protein, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR0363 or PR05723 through interaction with PR01387 and vice versa, method of linking a bioactive molecule to a cell expressing PR01387 using PR0363 or PR05723 as binding ligands and vice versa, and method of modulating the activity of PR01387 by binding with PR0363 or PR05723, and vice versa, whereby invention 140 is limited to PR0363 and invention 141 is limited to PR05723.

10. Claims: Invention 142: claims 1-28, 53-60,87-92,111-114, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR01114 (seq.ID.183), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to PR01114, chimeric protein comprising a portion corresponding to PR01114, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR03301 or PR09940 through interaction with PR01114 and vice versa, method of linking a bioactive molecule to a cell expressing PR01114 using PR03301 or PR09940 as binding ligands and vice versa.

and method of modulating the activity of PR01114 by binding with PR03301 or PR09940, and vice versa.

11. Claims: Invention 143 and 144: claims 1-28, 53-60,87-92, 111-114, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PRO3301 (seq.ID.507) or PR09940 (seq.ID.509), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to said protein, chimeric protein comprising a portion corresponding to said protein, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PRO3301 or PRO9940 through interaction with PR01114 and vice versa, method of linking a bioactive molecule to a cell expressing PR01114 using PR03301 or PR09940 as binding ligands and vice versa, and method of modulating the activity of PRO1114 by binding with PRO3301 or PR09940, and vice versa, whereby invention 143 is limited to PR03301 and invention 144 is limited to PR09940.

12. Claims: Invention 145: claims 1-28,61-69,93-98,115-118, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR01181 (seq.ID.355), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to PR01181, chimeric protein comprising a portion corresponding to PR01181, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR07170, PR0361 or PRO846 through interaction with PRO1181 and vice versa. method of linking a bioactive molecule to a cell expressing PR01181 using PR07170, PR0361 or PR0846 as binding ligands and vice versa, and method of modulating the activity of PR01181 by binding with PR07170, PR0361 or PR0846, and vice versa.

Claims: Inventions 146-148: claims 1-28,61-69,93-98.

115-118, all partially and claims 4 and 13 as far as applicable

Isolated nucleic acid having at least 80% sequence homology to a polynucleotide sequence encoding PR07170 (seq.ID.513). PRO361 (seq.ID.515) or PRO846 (seq.ID.517), vector comprising said nucleic acid, host cell comprising said vector, method of producing said protein using said host, isolated protein having at least 80% homology to said protien, chimeric protein comprising a portion corresponding to said protein, antibody against said protein, the isolated extracellular domain of said protein or a protein with at least 80% homology thereto, and said isolated protein lacking its signal peptide or a protein with at least 80% homology thereto. Method for detecting PR07170, PR0361 or PRO846 through interaction with PRO1181 and vice versa. method of linking a bioactive molecule to a cell expressing PRO1181 using PRO7170, PRO361 or PRO846 as binding ligands and vice versa, and method of modulating the activity of PR01181 by binding with PR07170, PR0361 or PR0846, and vice versa, whereby invention 146 is limited to PR07170, invention 147 is limited to PRO361, and invention 148 is limited to PRO846.

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